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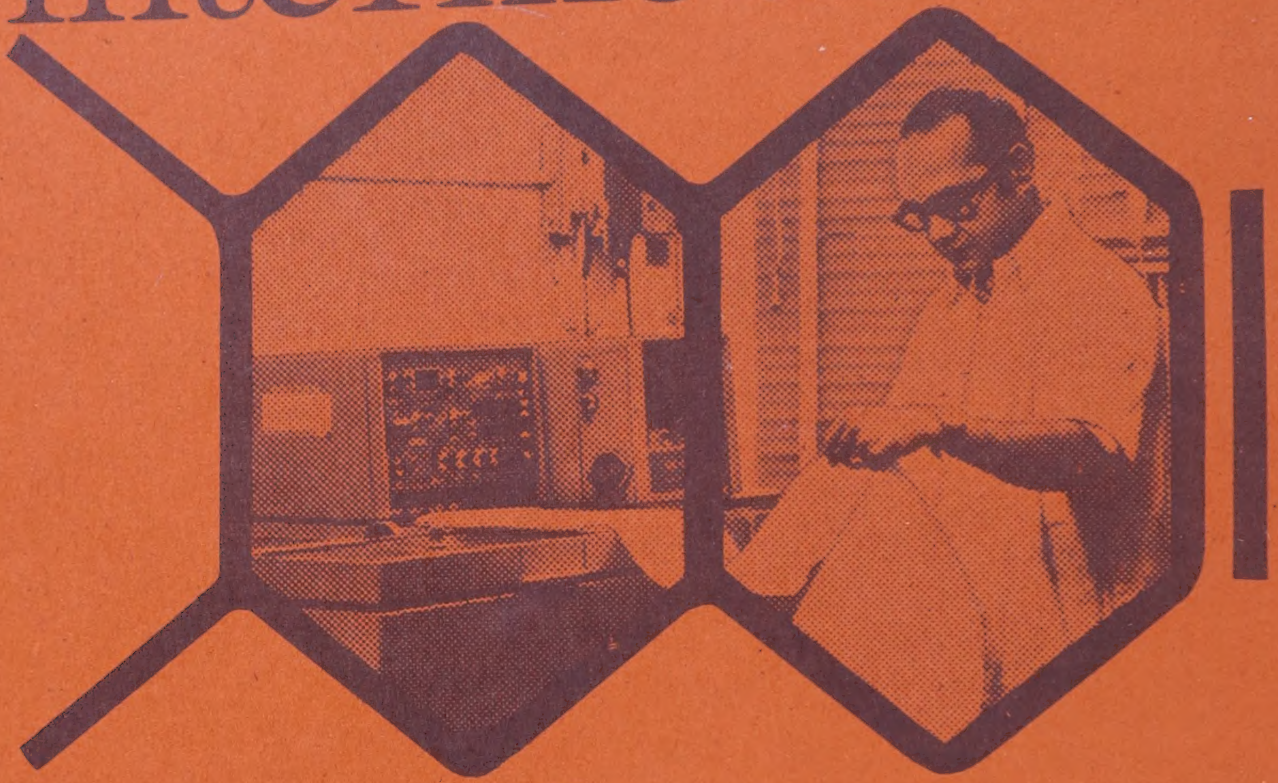

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Communications

Reaction of Tetrahydropyranyl Ether of 1-Bromomethyl-2-naphthol with Tetrachlorocatechol—Structures of Novel Products

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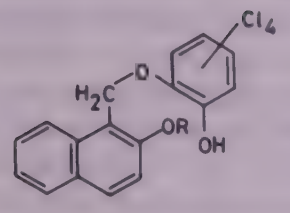
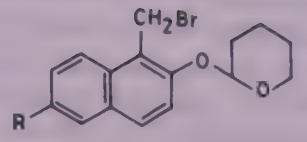
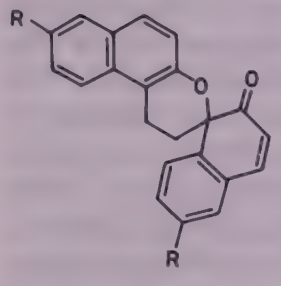
Structures of novel products obtained in the reaction of tetrahydropyranyl ether of 1-bromomethyl-2-naphthols (**2**) with tetrachlorocatechol in the presence of anhydrous potassium carbonate in acetone have been assigned as **5** and **6** on the basis of spectral data. Structure **5b** has been confirmed by X-ray crystal structure analysis.



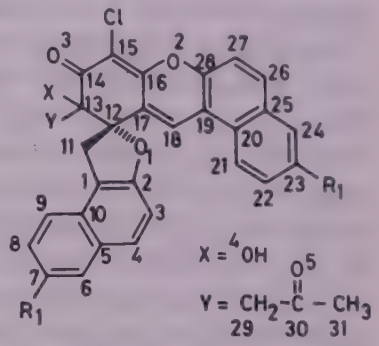
(1) R=H
(3) R=



(2a) R=H
(2b) R=Br



(4a) R=H
(4b) R=Br



(5a) R_1=H } X is α
(5b) R_1=Br } Y is β
(6a) R_1=H } X is β
(6b) R_1=Br } Y is α

In connection with mechanistic studies on the unusual oxidative rearrangement of substituted 2-naphthols and oxydiphenols[1], we were interested to synthesise the substituted naphthol (**1**) with a view to studying its behaviour towards oxidants like *o*-chloranil and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). It was planned to synthesise **1** by condensation of the tetrahydropyranyl ether of 1-bromomethyl-2-naphthol (**2a**) with tetrachlorocatechol in the presence of anhydrous potassium carbonate in acetone followed by removal of tetrahydropyranyl group of the resulting product (**3**).

N-Bromosuccinamide bromination of tetrahydropyranyl ether of 1-methyl-2-naphthol gave **2a** [PMR (60 MHz; CCl_4) δ 1.4-2.3 (6H, *m*), 3.3-4.0 (2H, *m*), 5.0 (2H, *s*), 5.5 (1H, br.*t*) and 7.1-8.0 (6H, *m*)]. The condensation of **2a** (1 mol) with tetrachlorocatechol (1 mol) was carried out in dry acetone in presence of anhydrous potassium carbonate (3 mol) under refluxing conditions for 36 hr. The products obtained, after usual work up, were separated into alkali soluble and neutral fractions. The required **3** was not detected in the alkali soluble fraction which contained mainly tetrachlorocatechol. Careful column chromatography of the neutral fraction (42% yield) followed by preparative TLC led to three distinct yellow products, the least polar being characterised as the dimer of 1,2-naphthoquinone-1-methide (**4a**) and the identity finally confirmed by comparison with an authentic sample[2].

Medium polar compound (A) analysed* for $C_{31}H_{21}ClO_5$ (M^+ 508.107448; calc. 508.107741) and exhibited IR spectrum peaks corresponding to a hydroxyl and two carbonyl groups one of which was conjugated ν_{max} (nujol): 3350, 1715 and 1675 cm^{-1}]. The characteristic features in PMR are: One D_2O exchangeable proton at δ 6.7 (OH); two *ABq* centred at 2.79 ($\Delta\nu_{AB}$ = 124.2 Hz, J_{AB} = 16.0 Hz) and 3.65 ($\Delta\nu_{AB}$ = 91.8 Hz, J_{AB} = 16.0 Hz) indicating presence of two methylene groups with non-equivalent protons; a three-proton singlet at 2.32 due to an acetyl group and signals between 7.3 and 8.2 due to aromatic protons. The mass spectrum of compound (A) exhibited a prominent peak at *m/z* 450 (M − 58) corresponding to an elemental composition of $C_{28}H_{15}ClO_4$ (high resolution: observed mass 450.066707; calc. 450.065879) and resulting from loss of an acetone molecule from M^+. This suggested the presence of an acetonyl side chain confirming the PMR observation.

*All new compounds reported here gave satisfactory elemental analysis.

The spectral properties [MS: m/z 508 (M^+, ^{35}Cl); IR (nujol): 3400, 1710 and 1670 cm^{-1}; PMR (270 MHz; $CDCl_3$): δ 2.2 (3H, *s*), 3.08 (2H, *ABq*, $\Delta\nu_{AB}$ = 145.8 Hz, J_{AB} = 16.0 Hz), 3.72 (2H, *ABq*, $\Delta\nu_{AB}$ = 202.5 Hz, J_{AB} = 16.0 Hz), 4.8 (1H, OH) and 7.26-8.10 (13H, *m*)] of the most polar compound (B)[b] are very similar to those of compound (A) indicating that these two compounds could be diastereomers. Based on these spectral data and on mechanistic grounds, the diastereomeric structures (**5a**) and (**6a**) have been tentatively assigned[c] to compounds (A) and (B) respectively. Structures **5a** and **6a** could not be confirmed by X-ray analysis as none of them gave good crystals.

A similar condensation reaction of compound (**2b**) with tetrachlorocatechol in acetone led to the corresponding products (**5b**) [MS: m/z 664 (M^+; ^{35}Cl; ^{79}Br); IR (nujol): 3440, 1715 and 1670 cm^{-1}; PMR (270 MHz; $CDCl_3$): δ 2.33 (3H, *s*), 2.73 (2H, *ABq*, $\Delta\nu_{AB}$ = 129.6 Hz, J_{AB} = 16.2 Hz), 3.60 (2H, *ABq*, $\Delta\nu_{AB}$ = 81.0 Hz, J_{AB} = 16.2 Hz), 6.75 (1H, OH) and 7.25-8.04 (11H, *m*)] and (**6b**) [MS: m/z 664 (M^+; ^{35}Cl; ^{79}Br); IR (nujol): 3460, 1715 and 1670 cm^{-1}; PMR (270 MHz; $CDCl_3$): δ 2.24 (3H, *s*), 3.09 (2H, *ABq*, $\Delta\nu_{AB}$ = 143.1 Hz, J_{AB} = 16.2 Hz), 3.71 (2H, *ABq*, $\Delta\nu_{AB}$ = 191.7 Hz, J_{AB} = 16.2 Hz), 4.79 (1H, OH) and 7.26-8.04 (11H, *m*)] along with the dimer (**4b**). The structures (**5b**) and (**6b**) were evident from their spectral properties which were very similar to those of the corresponding (**5a**) and (**6a**). Results obtained from X-ray structure analysis of **5b** are in full agreement with the structure proposed.

Crystal data of compound[d] (**5b**)

$C_{31}H_{19}ClBr_2O_5.\frac{1}{2}\ C_6H_6$, M = 670.4 monoclinic; space group C2/c; a = 29.917(4); b = 14.931(1); c = 15.002(1) Å; β = 119.20(1)°; Z = 8; D_c = 1.522 g cm^{-3}; MoK_α radiation; λ = 0.7107 Å; and μ = 30.8 cm^{-1}. The density of the crystal could not be measured owing to paucity of crystals. The structure was solved by direct methods using the programme MULTAN-78[4] in the space group C2/c. The centrosymmetric space group was chosen as the distribution of normalized structure factors was clearly centric. A difference electron density map showed clearly that a benzene molecule is at the crystallographic centre of symmetry. Least squares refinement of atomic and positional parameters (anisotropic Br and Cl; isotropic C and O) led to a R-value of 5.8% for 844 statistically significant reflexions [$|F| > 3.0\,\sigma(|F|)$] measured using an Enraf-Nonius CAD-diffractometer (Zr-filtered MoK_α radiation, $\omega/2\theta$ scan mode). A perspective view of **5b** is shown in Fig. 1. The calculated torsion angle O(1)-C(12)-C(13)-O(4) of −63.1° corresponds to *cis*-configuration.

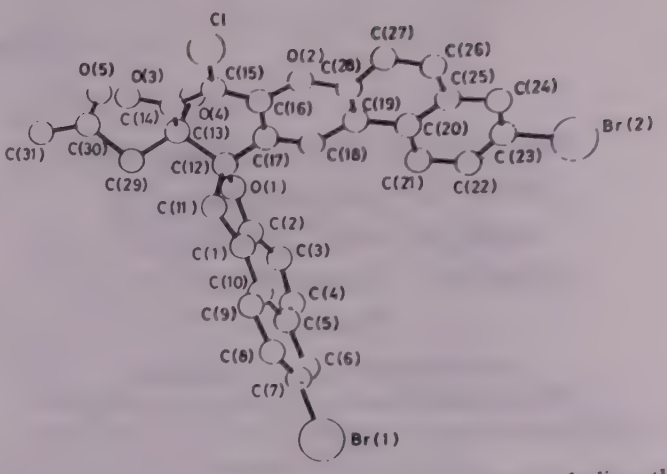


Fig. 1—A perspective view of the molecule (**5b**) (excluding the benzene molecule of crystallisation)

It is not very clear at present how these novel polycyclic compounds in the one-pot reaction are formed. Perhaps, two molecules of 1,2-naphthoquinone-1-methide initially formed[e] by cleavage[f] of the pyranyl ether, undergo Michael addition with tetrachlorocatechol, followed by stepwise removal of chlorine atoms and aldol condensation with acetone. The generality and mechanistic aspects of this interesting reaction are under study.

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[b]Relative amounts of these three products **4a**, **A** & **B** are in the ratio 11:1:2 and compounds A & B are racemic mixtures.

[c]Several other possible alternate structures were ruled out on the basis of a detailed study of the ^{13}C n.m.r. spectra in presence of trichloroacetyl isocyanate[3].

[d]The atomic coordinates for this work are available with one of the authors (TNG).

[e]Formation of this intermediate was evident from the isolation of its dimer (**4**).

[f]Definite experimental evidences have been obtained to show that pyranyl ether is cleaved under basic conditions only.

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Oxidation of Vicinal Diols by Bis(tri-*n*-butyltin) Oxide & Bromine

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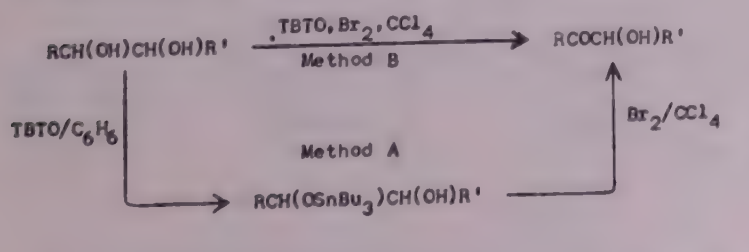
Bis(tri-*n*-butyltin) oxide and bromine oxidise vicinal diols to the corresponding diketones in carbon tetrachloride medium.

Several methods are available for the oxidation of vicinal diols to carbonyl compounds[1-9]. All these methods invariably result in the cleavage of carbon-carbon bond. We were interested in developing a reagent for the oxidation of vicinal diols to keto alcohols without the cleavage of C−C bond. A literature search revealed that one of the interesting applications of a commercially available fungicide, bis(tri-*n*-butyltin) oxide (TBTO) is in the conversion of secondary alcohols and aromatic primary alcohols into the corresponding carbonyl compounds[11,12]. In this communication we wish to report that the reagent TBTO/bromine in carbon tetrachloride medium brings about oxidation of vicinal diols to keto alcohols without the cleavage of C−C bond. This method is simple and the conditions employed are mild and neutral.

Two methods have been adopted for the oxidation of vicinal diols by TBTO/bromine reagent. In the first method (A) the diol is converted into the tributylstannyl alkoxide (TBSA) by reacting with a calculated amount of TBTO and removing water azeotropically. Subsequently the alkoxide is oxidised by bromine in carbon tetrachloride. In the second method (B) the diol, TBTO and bromine are reacted in the same solvent (see Scheme 1).

The following are the salient features of the reaction: (i) the oxidation product is the keto alcohol; (ii) the formation of only mono-stannylated intermediate is observed even with excess of TBTO; and (iii) the resulting keto alcohol is oxidised to 1,2-diketo product only.



TBTO = $(Bu_3Sn)_2O$; (I) R = C_6H_5; R' = H; (II) R = R' = C_6H_5

SCHEME 1

As typical example, the experiment with phenylethyleneglycol is described here.

Method-A: Phenylethyleneglycol (1.4 g, 10 mmol) and TBTO (3 g, 5 mmol) were refluxed together in dry benzene (70 ml) with simultaneous azeotropic removal of water using a Dean-Stark apparatus. Tributylstannyl alkoxide (TBSA) of phenylethyleneglycol formed was isolated after removing benzene in a rotary evaporator followed by distillation. The TBSA (0.86 g, 2 mmol) and bromine (AR, 0.32 g, 2 mmol) were magnetically stirred in dry carbon tetrachloride under pure dry nitrogen atmosphere at room temperature for 2 hr. The progress of the reaction was monitored by TLC (ether-*n*-hexane, 1:2; silica gel). Carbon tetrachloride was distilled off and the product was extracted with dry ether. A 5% aqueous ammonium fluoride (40 ml) was added and the insoluble tributyltin fluoride filtered off. The ketone obtained after evaporation of ether was recrystallised from *n*-hexane (yield, 1 g) (Table 1).

Method B: To a mixture of phenylethyleneglycol (1.4 g, 10 mmol) and TBTO (3 g, 5 mmol) dissolved in dry carbon tetrachloride, bromine (AR, 1.6 g, 10 mmol) was added dropwise under dry nitrogen atmosphere. The contents were stirred for 3 hr at room temperature. The progress of the reaction was monitored by TLC (ether-*n*-hexane, 1:2; silica gel). At the end of the reaction carbon tetrachloride was distilled off and the residue dissolved in dry ether. A 5% aqueous ammonium fluoride (40 ml) was added and the insoluble tributyltin fluoride filtered off. The ketone obtained after evaporation of ether was recrystallised from *n*-hexane (yield, 0.9 g) (Table 1).

Attempts to prepare the TBSAs of tetramethylethyleneglycol and tetraphenylethyleneglycol were

Table 1 — Isolated Yields of TBTO-Bromine Oxidation Products

Substrate	Yield (%) of TBSA	Yield (%) of diketone		m.p. °C (2,4 DNP of diketone)
		Method A	Method B	
Phenylethyleneglycol	87	72	63	85* (86)[13]
1,2-Diphenylethyleneglycol	56	67	45	244 (245)[14]
Benzoin	63	71	74	187 (189)[14]

*m.p. of hydroxyacetophenone.

not successful. This could be ascribed to the steric crowding of the bulky alkyl/aryl groups inhibiting the formation of alkoxides.

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Stereochemical Aspects of the Bose Reaction for α-Amino-β-lactam Synthesis†

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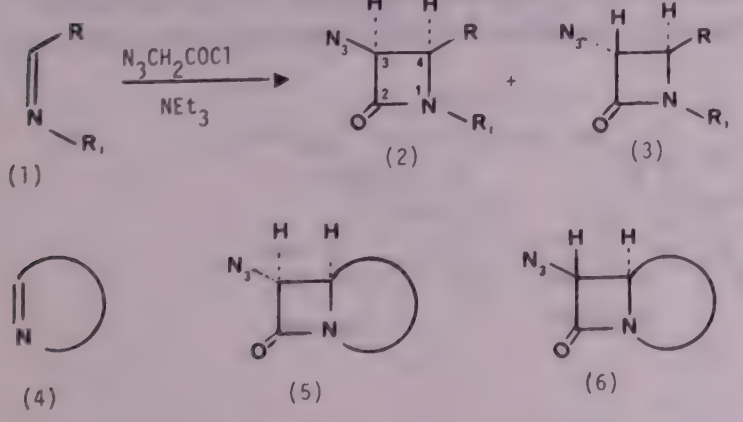
Received 4 *August* 1986

Stereochemical aspects of the Bose reaction (formation of α-azido-β-lactams from an activated form of azidoacetic acid and imino compounds in the presence of a base) are examined. Substituted β-lactams prepared by stereocontrolled synthesis (including enantiospecific synthesis) are shown to be useful intermediates for β-lactam antibiotics, sugars, alkaloids and other natural products. A stereospecific synthesis of an optically active 3-aminosugar related to gentosamine starting from a β-lactam synthon is described.

The reaction of azidoacetyl chloride (or a suitable carboxyl-activated form of azidoacetic acid) with schiff bases (**1**) or imino compounds (**4**) to form monocyclic (**2**, **3**) or polycyclic (**5**, **6**), α-azido-β-lactams (3-azido-2-azetidinones) has been termed the Bose reaction[1].

This reaction was described in 1966 by Bose and coworkers[2-5] in the course of their development of the total synthesis of 6-epi-penicillin (**7**). These authors were interested in a facile synthesis of α-amino-β-lactams which could be subsequently acylated to α-amino-β-lactams. The azido group serves as a latent amino function in this synthesis because it is unaffected during many chemical alterations of the β-lactam substituents but is easily reduced to an amino group under chemical as well as catalytic conditions without disrupting the β-lactam ring.

The Bose reaction has proved very useful for the total synthesis of a number of classical as well as non-classical β-lactam antibiotics and a variety of other heterocycles[6,7].



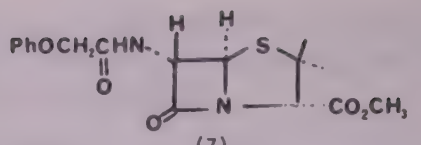
†Paper presented at the Symposium on the Chemistry of Natural Products organized at Stevens Institute of Technology to felicitate Prof. Ajay K. Bose on the occasion of his 60th birthday.

In the Bose reaction two asymmetric centers are created from two achiral moieties. The resulting β-lactam, therefore, is (+/−)-*cis* and/or (+/−)-*trans*. In the special case when either C-3 or C-4 has two identical substituents, the number of isomers is reduced to one racemic pair. If, however, the imino compound is optically active, diastereomers which are optically active would be formed; should the ring closure prove to be specific, a single enantiomer of a specific geometry would result. In case of the Bose reaction with a cyclic imino compound, additional steric considerations have to be taken into account. These variations which have been observed in the course of detailed studies on α-amino-β-lactam synthesis will be described in the following sections.

Cis- and *trans*-β-lactams

In general, it has been found[3] that the reaction of acyclic imines with azidoacetyl chloride in the presence of triethylamine in benzene gives two isomeric β-lactams: *cis*-(**2**) and *trans*-(**3**). The relative proportion of *cis*- and *trans*-β-lactams was observed to be dependent in some cases on the sequence of addition of reactants. Thus, when a solution of azidoacetyl chloride in methylene chloride was added to a solution of benzylideneaniline and triethylamine, either at room temperature or below, the *cis* to *trans* ratio of the β-lactams obtained was 3:1, in contrast, to the *cis*/*trans* ratio 1:3 when triethylamine was added to a solution of the imine and acid chloride[3]. The possibility of interconversion of isomeric *cis* and *trans* α-azido-β-lactams under the conditions of the experiment was ruled out on the basis of NMR experiments.

In determining the steric course of β-lactam formation, the structure of the schiff base also plays a role that is not easily rationalized. From schiff bases derived from furfuraldehyde, cinnamaldehyde or methyl glyoxalate, only *cis*-β-lactams are obtained



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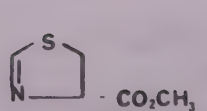
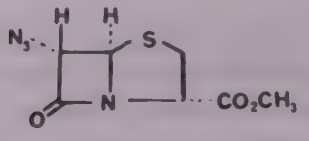


(8)



(9)

when annelation is conducted with azidoacetyl chloride (or equivalent) and triethylamine under the various reaction conditions described.

On the other hand, when azidoacetyl chloride reacts with a thioimidate the azido group is *trans* to the thio group in the β-lactam formed. Taking advantage of this, *cis*-β-lactams have been prepared by desulfurization through hydrogenolysis[8] (hydrogen and Raney nickel). If the catalyst is too reactive, scission of the $N-C_4$ bond can also take place leading to the arylamide of a β-aryl-α-amino acid.

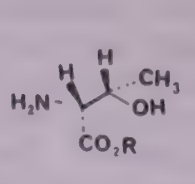
A fused β-lactam of the type of penicillin or cephalosporin can have either the *cis* or *trans* configuration of the β-lactam ring. Bose *et al.*[4] showed that the reaction of azidoacetyl chloride with the thiazoline (**8**) in the presence of triethylamine was stereospecific and afforded a single isomer of the penam (**9**). The C-5 hydrogen at the ring junction and the carboxyl group at C-3 are *cis* to each other—thereby assuming the less sterically hindered exo-positions. As observed before, the azido group at C-6 places itself *trans* to the thio group at C-5 in the fused β-lactam formed. Thus, the configuration of the carboxyl group in **8** determines the stereochemistry of the rest of the bicyclic system. Vanderhaeghe *et al.*[9] repeated the synthesis of Bose and coworkers[4] and prepared an optically pure 6-epi-penicillin ester which they converted into an optically active natural penicillin. The Merck group[10] has synthesized penicillins, cephalosporins and various oxa- and carba-analogues using the Bose reaction.

Optically active β-lactams

There are two potential centers of asymmetry, namely C-3 and C-4, in a 2-azetidinone. The wrong absolute configuration at either or both of these centers in a monocyclic or bicyclic β-lactam can reduce the activity of a β-lactam antibiotic to the vanishing point. The Bose reaction can lead to chiral β-lactams with high diastereoselectivity if the imino component is chiral in nature. For preparing optically pure β-lactams Bose and coworkers[11-15] selected imines derived from threonine as the starting material since this amino acid is readily available in both enantiomeric forms. D-Threonine (**10**) was converted into the ester (**11**) which on condensation with *trans*-cinnamaldehyde afforded aldimine (**12**) in excellent yield. Reaction of **12a** (R=H) with azidoacetyl chloride (or other carboxyl activated azidoacetic acid) in the presence of triethylamine produced two diastereomeric *cis*-β-lactams (**13a**) and (**14a**), in nearly equal amounts. Lack of diastereofacial selectivity in the annelation of **12** could be ascribed to its almost planar geometry caused by strong hydrogen bonding between the ester carbonyl group and the β-hydroxyl group. Nearly equal ease of access from either *re* or *si* face would then lead to annelation without strong diastereoselectivity during the creation of new chiral centers at C-3 and C-4 of the 2-azetidinones.

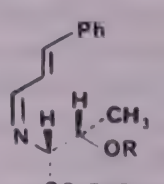
When phenylserine was substituted for threonine as the amine component of the schiff base, the two faces were not equally accessible because of the bulk of the phenyl group; in consequence, substantial diastereoselectivity (80:20) was observed during annelation. It is thus logical to expect a high diastereoselectivity if the hydroxyl group of the imine is blocked by a bulky group.

Tenneson and Belleau[16] have observed that when the hydroxyl group of D-threonine was protected by t-butyldimethylsilyl (TBDMS) ether formation, the two

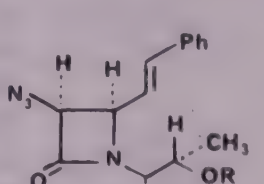


(10) R=H

(11) R = PNB



(12)



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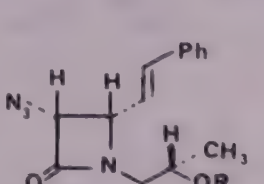


(14)

PNB = $CH_2C_6H_4NO_2(p)$

TBDMS = $Si(t\text{-}Bu)Me_2$

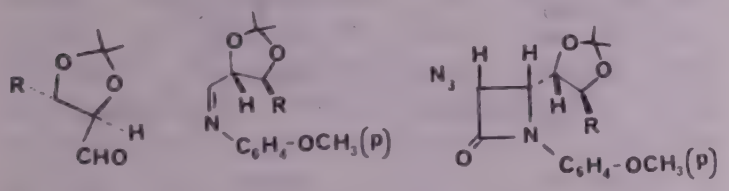
TPS = $SiPh_3$

	R	13/14
(a)	H	50/50
(b)	TBDMS	90/10
(c)	TPS	95/5

diastereomers were obtained in 90:10 ratio. Bose *et al.*[11–14] showed that the use of the very bulky triphenylsilyl (TPS) ether derivative of D-threonine provides very high diastereoselectivity in the annelation step. After desilylation the two diastereomers (**13** and **14**) could be separated by column chromatography.

Using a different approach Bose *et al.*[13,14] have achieved an enantiospecific synthesis of 3,4-disubstituted-2-azetidinones. They converted (+)-glyceraldehyde acetonide (**15a**) into an unstable aldimine (**16a**) which on reaction with activated azidoacetic acid gave a single optically pure β-lactam (**17a**) in 60% yield. This synthesis was reported independently by Hubschwerlen and Schmidt[15] and Bose *et al.*[13].

To investigate the effect of another chiral center on the diastereofacial selectivity of the β-lactam formation reaction, the aldehyde (**15b**) was prepared from D-threonine[13,14]. At the end of the same synthetic sequence, this aldehyde too led to a single optically pure *cis*-β-lactam (**17b**). These results show that the second chiral center in the aldehyde may not exercise any strong influence on the annelation reaction.



(15) (16) (17)

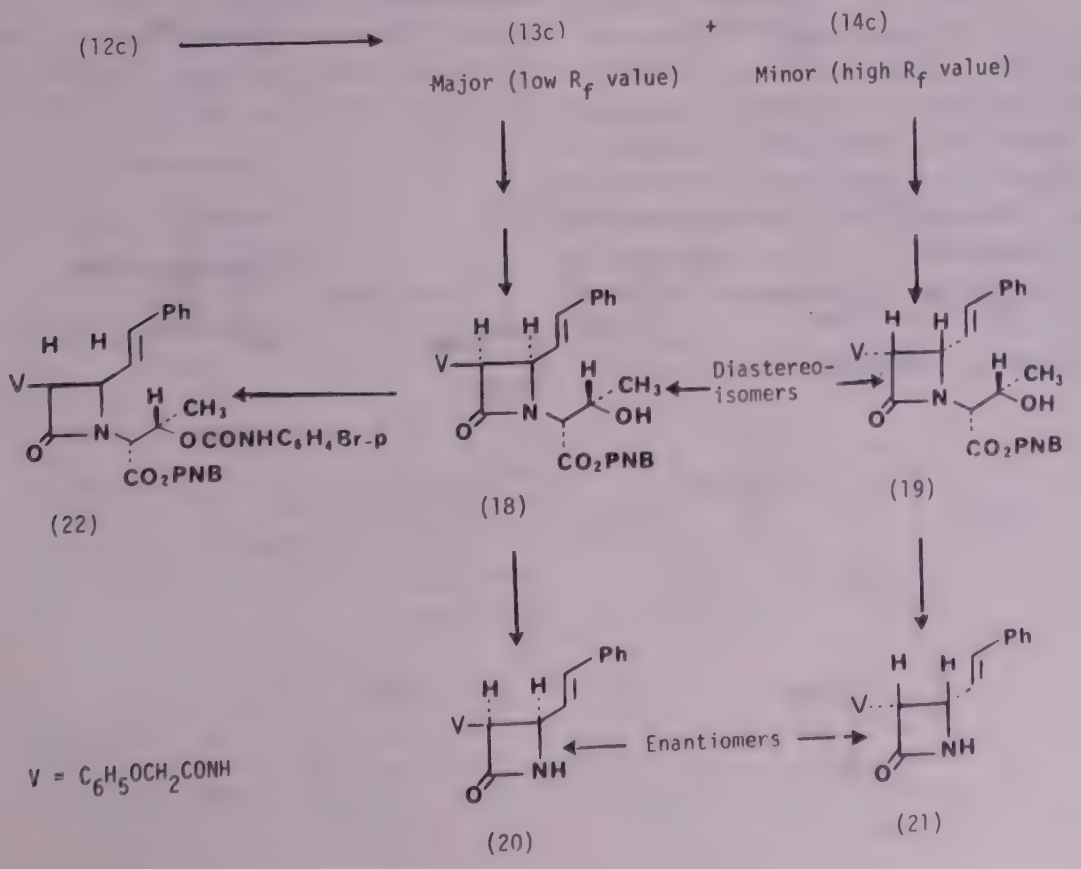
a. R=H; b. R=CH_3

Absolute configuration

The single crystal X-ray diffraction technique is the method of choice for determining the absolute configuration of some of the optically active β-lactams synthesised by the Bose reaction. But, none of these compounds produced suitable crystals. This problem was resolved, however, when it was found that the *p*-bromophenylurethane of the *racemic form* of the β-lactam (**22**) yielded crystals that were satisfactory for X-ray diffraction. Interestingly, studies on this racemic material allowed the determination of absolute configuration of enantiomeric forms of **13c** and **18** prepared from D-threonine.

The inter-relationship of the β-lactams studied is shown in Scheme 1. The key to the success of this approach for determination of absolute configuration is the fact that the (*S*)-configuration of the methylcarbinol group derived from D-threonine remains unaltered during the chemical transformation of **12c** into **22**. That ORTEP diagram of the *p*-bromophenylurethane of DL-**22**, was selected which had the (*S*)-absolute configuration at the carbinol carbon (i.e. C-3'); the configuration at C-3 on this diagram was (*S*) and at C-4, (*R*). The absolute

Scheme 1



configurations of **13**, **18** and **20** are thus as shown by the stereostructures in Scheme 1.

The circular dichroism (CD) curves for **20** and **21** were found to be mirror images of each other; hence, the absolute configuration at C-3 and C-4 in **21** (and therefore in **19** and **14** also) must be (*R*) and (*S*), respectively.

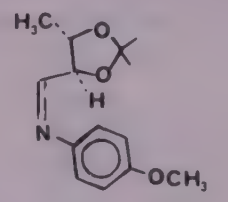
The absolute configuration of **17a**—prepared from the schiff base (**16a**) derived from D-glyceraldehyde—was determined by chemical degradation[15]. Through a series of reactions (Scheme 2) the β-lactam (**17a**) was converted into the N-unsubstituted product (**23**). The slow moving diasteroisomer (**13a**) of known absolute configuration obtained by the reaction of azidoacetyl chloride and schiff base (**24a**) was converted into **24b** and then oxidized to **25** with ruthenium tetroxide. The specific rotation of **24** and **25** and their CD curves show that they are mirror images of each other (see Scheme 2). Since no change of configuration at C-3 and C-4 can be expected under the reaction conditions, the stereostructure of **23** must represent its absolute configuration. This establishes the absolute configuration of **24** and therefore of **17a** to be as shown.

The optically active β-lactam (**17b**) [prepared from the acetonide (**15b**) derived from D-threonine] failed to produce crystals suitable for X-ray studies. However, crystals of the racemic β-lactam (**27**) derived from DL-threonine were satisfactory and X-ray diffraction studies led to the assignment of the absolute configuration shown for **17b** using the same approach as for DL-(**22**).

In summary, in order to match the absolute configuration of natural penicillin at the β-lactam carbons, the Bose reaction should be conducted with an optically active schiff base derived from one of the following: (i) the acetonide of L-glyceraldehyde and an achiral amino compound; (ii) triphenylsilyl ether of a D-threonine ester and an achiral aldehyde.

Scope of the Bose reaction

In the early stages of the development of the Bose reaction, penicillins and cephalosporins were the goals of most laboratories. In the belief that other β-lactam systems besides penams and cephams have the potential for biological activity. Bose and coworkers[17] devised synthetic strategies based on the visualization



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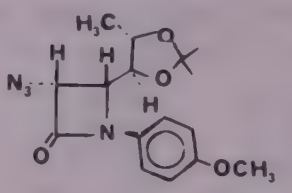
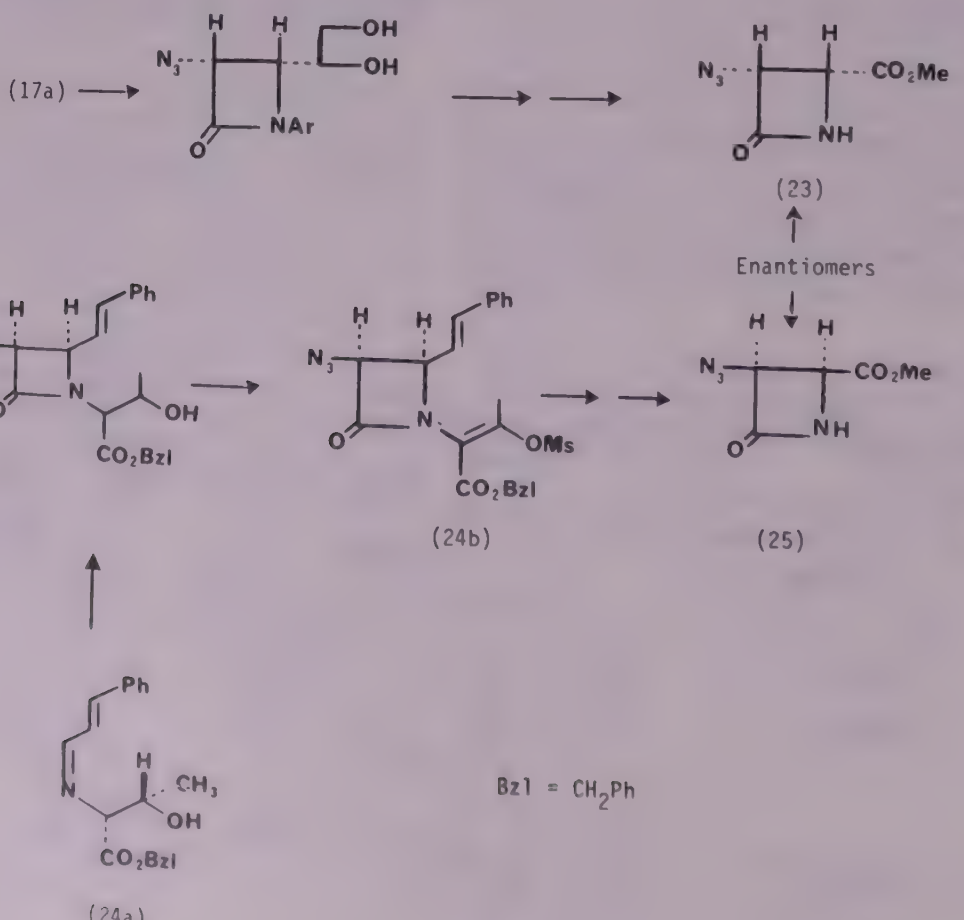


(27)

Scheme 2



of the β-lactam antibiotic molecule into three segments: the head, the body and the tail (**28**). While literally hundreds of penicillin and cephalosporin derivatives have been prepared by the modification of the tail portion almost no attention was paid to the manipulation of the head portion till late sixties.

After the successful, short synthesis of the methyl ester of epi-penicillin (**7**), Bose and coworkers started an extensive investigation on the synthesis of various penam and cepham analogs[18,19]. Thus, reaction of azidoacetyl chloride with 5,5-dimethyl-2-phenyl-2-thiazoline-4-carboxylate (**29**) in the presence of triethylamine afforded 5-phenyl-6-azidopenam (**30**) in good yield which was eventually transformed to 5-phenyl-benzylpenicillin (**32**). In another communication the same authors described the synthesis of some 6-azidopenams[20]. Thus, the cyclic imine (**33**) on treatment with azidoacetyl chloride afforded the penam (**34**) in 70% yield. Reduction under catalytic conditions and subsequent treatment with phenoxyacetyl chloride led to a product (**35**) which did not contain the expected amide side chain. Spectral evidence as well as an independent synthesis established 3,3-dimethyl-6-phenoxy-5-phenylpenam as the structure for **35**. The formation of **35** can be rationalized by assuming the scission of β-lactam (**34**) to give the starting thiazoline (**33**) which is subsequently annelated to **35** by reaction with phenoxyacetyl chloride and triethylamine.

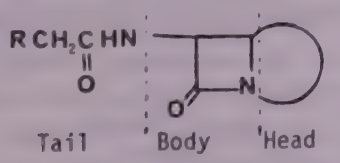
In 1968 a penicillin analog with a modified nucleus was reported by Bose *et al.*[21]. The cyclic intermediate (**36**) was prepared from α-bromoisobutyraldehyde, hydrogen sulfide, pentan-3-one and ammonia in good yield. Reaction of **36** with azidoacetyl chloride gave the *trans*-β-lactam (**37**) which was converted into a 2-thiaheptam[22] derivative (**39**). Although the thiazolines (**29**), (**33**) and (**36**) reacted with azidoacetyl chloride in a straightforward manner, thiazoline (**40**) showed little reactivity toward azidoacetyl chloride; in fact, only trace amounts of the 2-thiaheptam (**41**) were obtained. It was found, however, that under basic conditions **40** underwent isomerization to the 2-thiazoline (**42**) which reacted with azidoacetyl chloride to produce the 5-carbomethoxypenam derivative (**43**) in 86% yield[21].

The synthesis of the 1-azaheptam system was reported by Bose and coworkers[23] in 1973. They reacted 2-phenylimidazole (**44**) with an excess of azidoacetyl chloride in the presence of triethylamine. Spectroscopic evidence supported the 1-azaheptam structure (**45**) for the product.

In the case of cepham systems, first entry by using the Bose reaction was reported[2] in 1966. The dihydrothiazine (**46**) when treated with azidoacetyl chloride in the presence of triethylamine produced the cepham (**47**) in 55-60% yield. Reduction of the azido group followed by acylation placed an amide group at C-7 position. Compounds in which the sulfur atom at 1-position of cepham system is replaced by a methylene group, has been the subject of extensive research. Bose and coworkers[24-28] in their quest for developing newer β-lactam antibiotics have synthesised several compounds of this general structure. The appropriate cyclic imines (**49**) were prepared by Bischler-Napieralski reaction on the corresponding amides. Annelation of **49** under the Bose reaction conditions afforded the 7-azidooctam derivative (**50**) in excellent yield[26].

In another communication Bose *et al.*[28] have reported a total synthesis of other octams. Phenylalanine (**51**) was converted into the imine (**52**) by a multistep procedure. Treatment of **52** with azidoacetyl chloride led to the stereospecific formation of the octam (**53**). Conversion of the 7-azido group of **53** into the acylamino functionality followed by Raney-Ni hydrogenation generated the *cis*-β-lactam (**54**).

Extensive researches on the applications of the Bose



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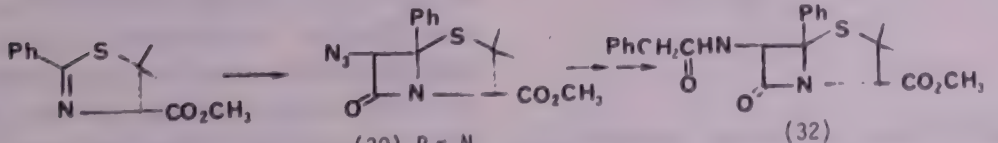
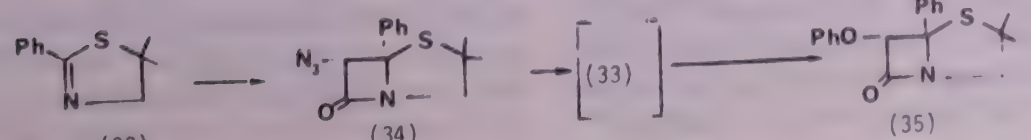
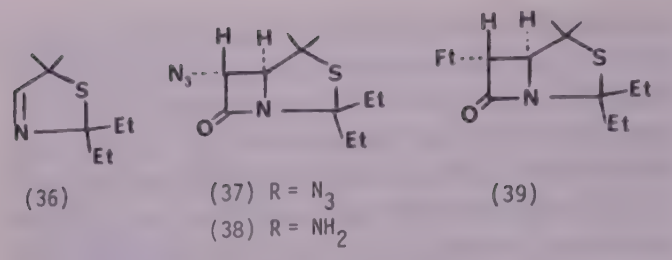


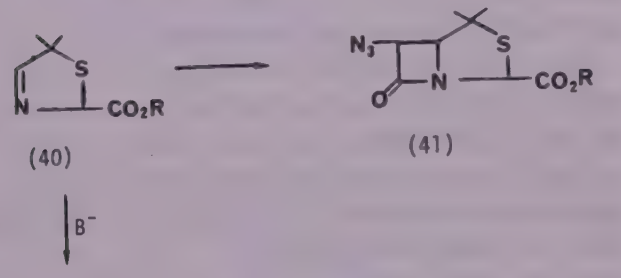
(29) (30) R = N_3 (31) R = NH_2 (32)



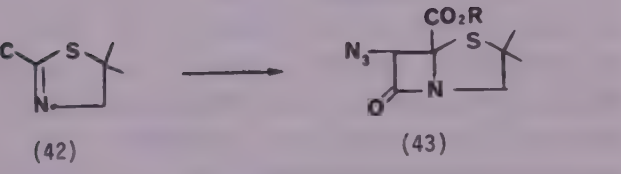
(33) (34) (35)



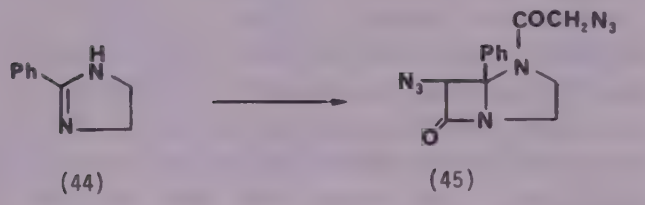
(36) (37) R = N_3 (38) R = NH_2 (39)



(40) (41)

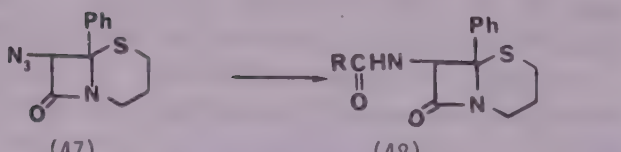


(42) (43)

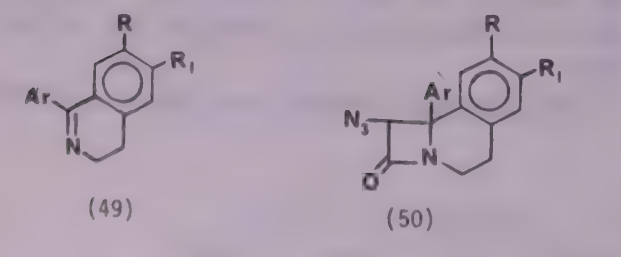


(44) (45)

(46)

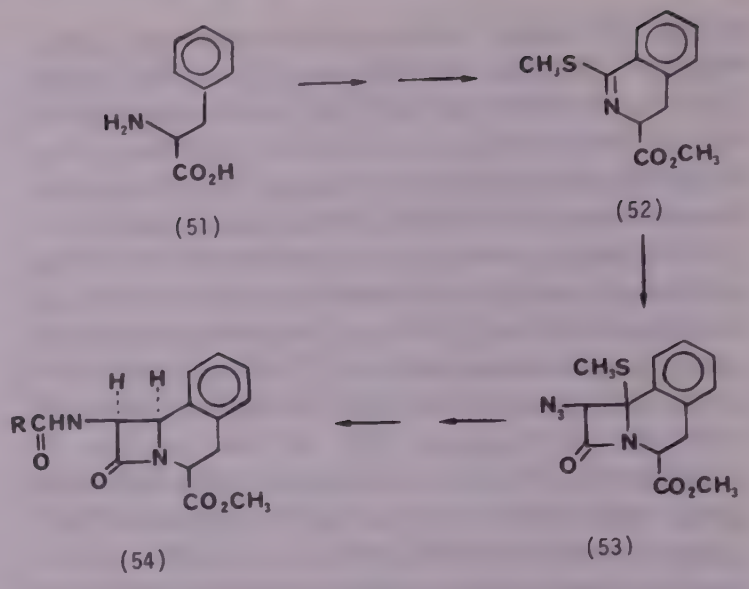


(47) (48)



(49) (50)

reaction to the synthesis of various natural and synthetic antibiotics have been carried out by many research groups. The Merck group[29–31] has utilized this reaction in their total synthesis of penicillin, cephalosporin, cephamycin and analogues. Bachi *et al.*[32,33] have applied this methodology in their relay synthesis of racemic penicillin. Synthesis of the heptam system was reported independently by Beecham[34], Merck[35] and Canadian[36] research groups. Bioisosteric replacement of a ring carbon atom by other atoms (e.g. S, O, N) would provide various analogues of penams and cephams. A large number of such compounds were prepared utilizing the Bose reaction as the pivotal synthetic step. Thus, the Smith Kline and French group[37] has reported the synthesis of 2-thiaheptam and the Merck group[38] has described the preparation of 1-oxaheptam in good yield. Similarly, the syntheses of other heptam derivatives, for instance, 2-aza- and 2-oxa-analogues, have been reported by Canadian[39], British[40] and American[41] research workers.



(51) (52) (53) (54)

A Japanese group[42] has synthesised various 3-trifluoromethylcephalosporin derivatives whereas researchers at Merck, Sharp and Dohme laboratories[29,43] have prepared cephamcycin and 3-arylcephalosporins. The Syntex research group[44] has also utilized the Bose reaction for the preparation of polycyclic cepham systems. Synthesis of the octam system has been the target of various pharmaceutical groups as well as academic institutions. Thus independent syntheses of variously substituted octams were reported by Shionogi[45], Bristol[46], McGill[47], Smith Kline and French[47], Merck, Sharp and Dohme[10,49], Israeli[50], and Glaxo[51] research groups. In each case the Bose reaction was utilized for the stereospecific construction of the β-lactam ring. Several other partial or total syntheses of various modified octam systems for instance, 1-oxa[52]-, 2-thia[53]-, 2-oxa[54,55]-, 2-aza[56]-, 3-oxa[57]-, 3-aza[58]- and 3-thia-octams[58], have also been reported.

β-Lactams as chiral synthons

The proclivity of appropriately substituted β-lactams for rearrangement is well known. Some years ago Manhas and coworkers[59] reviewed work done in their own laboratory and elsewhere on the use of β-lactams as synthons for a variety of heterocycles[59].

The easy availability of optically active β-lactams now allows access to many natural products (such as antibiotics, alkaloids, sugars, etc.) in either enantiomeric form. This approach is illustrated here by the synthesis of an amino sugar derivative via an optically active β-lactam.

Amino sugars are an important class of compounds as they form an integral part of several amino glycosides, macrolides and antibiotics and play critical roles in modern medicinal chemistry[60]. Recently Tsubomura and coworkers[61] have demonstrated antitumor activity of platinum(II) complexes of certain amino sugars.

In a publication Bose *et al.*[62] reported a synthetic approach to racemic amino sugars via β-lactams. Hauser and coworkers have also used 2-azetidinones for the synthesis of racemic[63] as well as optically active[64] N-benzoyldaunosamine. A stereospecific synthesis of an optically active 3-amino-3-deoxypyranose (**55**)—an analogue of gentosamine is described here.

Gentosamine (**56**) is a 3-amino sugar which is present in many compounds of the gentamicin-A complex[65], a potent antibiotic isolated from nature. DeShong *et al.*[66] recently reported the synthesis of 3-epi-gentosamine via nitrone cycloadditions.

A retrosynthesis of **55** is shown in Scheme 3. In order to prepare **55**, with 2*R*, 3*R*, 4*S* configuration, it is necessary to start with an optically active *cis*-β-lactam such as **57** with 3*R*, 4*S* configuration.

D-Glyceraldelyde acetonide (**15a**) prepared from D-mannitol[67] was used as a starting material. This aldehyde was allowed to react with *p*-anisidine to form the schiff base (**16a**). The reaction of **16a** with methoxyacetyl chloride in the presence of triethylamine afforded a single *cis*-β-lactam (**57**) in 54% yield. On the basis of chemical degradation[15] **57** was assigned the 3*R*, 4*S* configuration. Refluxing this β-lactam with 90% trifluoroacetic acid led to a single γ-lactone (**58**) (IR:CO at 1760 cm^{-1}) in 63% yield. The configuration of **58** was established by the application of Hudson's lactone rule and from NMR studies.

Reduction with diisobutylaluminium hydride (DIBAL-H) converted the lactone (**58**) into the amino sugar (**59**) which was characterized as its diacetyl derivative (**55**).

On the basis of its ^1H NMR spectrum and decoupling studies the stereostructure (**55**) was assigned to this amino sugar. The relative configuration of protons at C-1, C-2, C-3, C-4 and C-5 in **55** was clearly indicated by the ^1H NMR spectrum. The protons at C-2, C-3 and C-4 resonated at 4.00, 4.24 and 4.84 ppm, respectively. The C-2 and C-3 protons show a coupling constant of 9 Hz which is indicative of their diaxial (and hence *trans*) relationship. The C-3 and C-4 protons are also *trans* to each other [$J_{3,4}$ (ax-ax) = 9 Hz]. Of the two protons at C-5, the axially oriented proton appeared at 4.10 ppm and the equatorially oriented proton at 4.31 ppm.

The amino sugar (**55**) is an analogue of gentosamine. To obtain the other enantiomer of **55** the starting material would be derived from L-threonine. Work is in progress for the synthesis of optically active 2,3-diaminosugars from 3-azido-2-azetidinones.

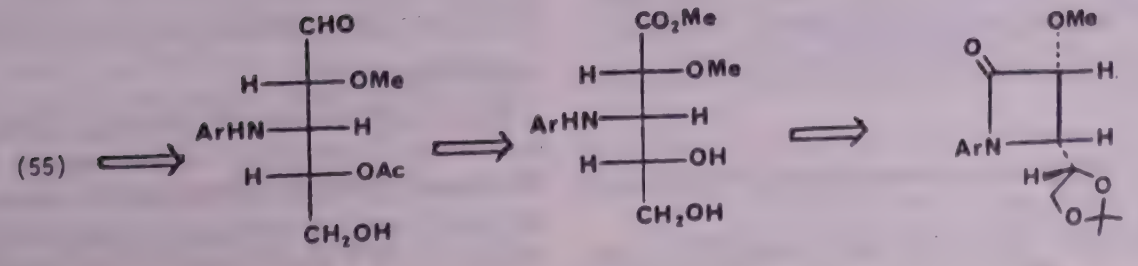
Experimental Procedure

M.ps were taken for samples in open capillary tubes (Mel. Temp. apparatus) and are uncorrected. IR spectra were obtained on a Perkin-Elmer 1310, spectrophotometer and PMR spectra were on a Varian EM-390 spectrometer or a Bruker WP200 SY spectrometer in appropriate solvents with $SiMe_4$ as an internal standard. Mass spectra (electron impact mass spectra, EIMS; chemical ionization mass spectra,

(55)

(56)

Scheme 3



(57)

(58)

(59) R = H
(55) R = OAc

Ar = p-anisyl

CIMS; and fast-atom bombardment, FAB) were recorded on a Perkin-Elmer RMU-7, CIMS Biospect Instrument and a Finnigan MAT 312 spectrometer. Elemental analyses were determined by Schwarzkopf Microanalytical Laboratory, Inc., Woodside, New York.

N-(p-Anisyl)-4-[(S)2',2'-dimethyl-1',3'-dioxolan-4'-yl]-methylene-imine (**16a**)

To a stirred solution of *p*-anisidine (1.23 g, 10 mmol) in ether (20 ml) at 0°C, was added 2,3-isopropyliodene-D-glyceraldehyde[67] (1.30 g, 10 mmol) in ether (20 ml). After 1 hr the reaction mixture was dried over anhydrous magnesium sulfate, filtered, and evaporated to give the crude schiff base (**16a**)' which was used as such in the next step.

cis-1-(p-Anisyl)-3-methoxy-4-[(S)-2',2'-dimethyl-1',3'-dioxalan-4'-yl] azetidin-2-one (**57**)

A solution of methoxyacetyl chloride (1.4 ml, 15 mmol) in dry methylene chloride (50 ml) was added dropwise, to a stirred solution containing **16a** (3.0 g, 13 mmol) and triethylamine (5.6 ml, 40 mmol) in dry methylene chloride (100 ml) under nitrogen atmosphere at −20°C. The reaction mixture was stirred overnight at room temperature and washed successively with aq sodium bicarbonate, brine and water. Organic layer was dried (Na_2SO_4), filtered and evaporated to give crude β-lactam (**57**) which was further purified by column chromatography (silica gel, hexanes- ethyl acetate, 7:3), yield 2.1 g, (54%), m.p. 93-94°, $[\alpha]_D^{26} = +142.4°$ (C, 0.5, MeOH); IR (KBr): 1750 cm^{-1}; PMR ($CDCl_3$); δ 7.69-6.87 (*dd*, *AB* pattern, 4H), 4.55 (*d*, *J* = 6 Hz, 1H), 4.36-4.09 (*m*, 4H), 3.8 (*s*, 3H), 3.6 (*s*, 3H), 1.52 (*s*, 3H), 1.31 (*s*, 3H); ^{13}CNMR ($CDCl_3$): 164.86, 156.50, 131.26, 119.56, 113.97, 109.68, 82.23, 77.14, 66.96, 61.82, 59.29, 55.39, 26.68, 24.98 ppm; CIMS (NH_3 reagent gas): m/z 308 $(M+1)^+$ (Found: C, 62.5; H, 6.9; N, 4.5%. $C_{19}H_{25}NO_5$ requires C, 62.5; H, 6.8; N, 4.6%).

2-*Methoxy-3-(4-methoxyphenylamino)-5-hydroxy-pentano-γ-lactone* (**58**)

The β-kactam (**57**) (3.1 g) was refluxed in 90% trifluoroacetic acid (20 ml) for 12 hr under nitrogen atmosphere. The reaction mixture was then cooled, dried *in vacuo* and the residue chromatographed over silica gel column. Elution with 1:1 ethyl acetate-hexane afforded pure lactone (**58**) (2.0 g, 64%) as an oil; $[\alpha]_D^{26} = +86.9°$ (C = 0.5, MeOH) in ($CDCl_3$): 3380, 1780, 1690, 1510, 1240 cm^{-1}; PMR ($CDCl_3$): δ 6.9-6.6 (*dd*, aromatic, 4H), 4.7 (*d*, *J* = 7.3 Hz, 1H), 4.45-4.25 (*m*, 2H), 4.0-3.7 (*m*, 4H), 3.75 (*s*, 3H), 3.6 (*s*, 3H); ^{13}C NMR ($CDCl_3$): 174.11, 153.11, 140.29, 115.20, 114.93, 82.00, 78.87, 60.57, 58.98, 58.77; 55.71 ppm; MS(FAB): *m/z* 268 $(M+1)^+$.

Gentosamine derivative (**55**)

A solution of diisobutylaluminium hydride (DIBAL) in hexane (15 ml, 0.015 mol) was rapidly added to a magnetically stirred, cold (−85°C; ethyl acetate-dry ice) solution of the lactone (**58**) (2.91 g, 11 mmol) in dry tetrahydrofuran (75 ml). The reaction mixture was maintained at −85°C for 5 hr and then quenched with methanol and the solvent evaporated to dryness. The residue was chromatographed on silica gel (100 g, ethyl acetate-methanol, 8:2) to give the sugar (**59**) (1 g, 35%); MS: *m/z*/270 $(M+1)^+$, **59** was converted into the diacetate (**55**) as described below:

The crude sugar (**59**) (1 g, 3.7 mmol) was acetylated by treatment with acetic anhydride (10 ml) and pyridine (10 ml). Stirring was continued for 24 hr at room temperature. The reaction mixture was dissolved in an aq $CuSO_4$ and extracted with ethyl acetate (4 × 50 ml). The combined ethyl acetate extract was washed with brine and dried (Na_2SO_4). Chromatography (silica gel, hexane-ethyl acetate, 1:1) afforded the gentosanine derivative (**55**) as a yellow oil (1.1 g, 73%): IR (neat): 2960, 1750, 1670, 1520, 1370, 1310, 1250 cm^{-1}; PMR ($CDCl_3$): δ 6.8-6.5 (*dd*, aromatic, 4H), 6.08 (*s*, 1H), 5.69 (*d*, *J* = 6 Hz, 1H), 4.84 (*m*, 1H), 4.31-4.00 (*m*, 4H), 3.64 (*s*, 3H), 3.51 (*s*, 3H), 1.96 (*s*, 3H), 1.74 (*s*, 3H); CIMS (NH_3 reagent gas): *m/z* 371 $(M+18)^+$.

Acknowledgement

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Fast Atom Bombardment Mass Spectrometry: A Powerful Technique for Study of Oligosaccharide Antibiotics†

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The application of fast atom bombardment mass spectrometry (FABMS) has been illustrated by a detailed study of the mass spectra of oligosaccharide antibiotics. The power of the method is demonstrated by determining the sequence of the sugar units in everninomicin (**1**) which is an octasaccharide with complex structure.

Fast atom bombardment mass spectrometry[1] (FABMS) is a new technique for obtaining high quality mass spectra of molecules which were previously difficult or impossible to study by ionization. A beam of fast moving argon or xenon atoms is allowed to bombard the surface of a target carrying the sample, which is usually dispersed in a glycerol solution or matrix. The fast moving atoms are produced in an "atom gun", for example, a saddle field ion source B11NF from Ion Tech: the source produces a beam of Ar^+ with energy in the 5-10 KeV range. These ions then pass through a collision chamber filled with argon gas at a pressure of 10^{-3} to 10^{-4} torr. Resonant charge transfer occurs in most cases with no loss of kinetic energy giving rise to accelerated inert gas atoms. Any residual Ar^+ ions that remain are usually removed by deflector plates.

The fast moving atoms then hit the surface of the sample dissolved in a liquid matrix (glycerol) giving rise to pseudomolecular ions which may provide $(M+H)^+$ and $(M+Na)^+$ in positive ion spectra. Although argon is a satisfactory inert gas, xenon gives a severalfold increase in ion intensity, which is possibly due to xenon's higher mass and enhanced momentum.

It has been observed by several investigators[2] that the optimum sensitivity of sample ions is achieved when the angle between the incident beam (fast moving atoms) and a perpendicular drawn to the probe surface is approximately 70 degrees. It also appears that the ion intensity is not dependent on the composition of the probe tip. Various metals and nonmetals have been employed as the probe tip (target); the most commonly used target material is copper or stainless steel on which the sample suspension in a liquid matrix (glycerol) is applied. An important step in obtaining satisfactory FAB spectra is sample preparation. A completely miscible solution of an organic sample in a liquid matrix[3,4] provides good FAB spectra in most cases. The most widely used matrix to date is glycerol, because it is a good solvent for dissolving many biologically active, polar compounds including their salts; its low volatility also ensures a relatively long flow of sample molecules to the surface for ionization. Other useful matrices are thioglycerol, diethanolamine, triethanolamine, polyethylene glycols, sulfolane, crown ether etc. In the case of many oligosaccharide antibiotics, the best results were obtained using glycerol-thioglycerol mixture as a matrix[3] and dimethyl sulfoxide as a solvent.

FAB technique is very similar to another condensed state ionization method, SIMS[5] (Secondary Ion Mass Spectrometry). With SIMS a fast beam, as for example argon ion, is directed onto the target containing the sample and generates secondary ions of the sample molecules.

The mechanism of ion formation in FAB process has been the subject of considerable speculation[6-8]; whether it is a surface technique or a direct desorption of precharged species from the condensed phase still remains under investigation. Acid treatment of a zwitterionic compound results in a substantial increase in sensitivity of the pseudomolecular ion $(M+H)^+$.

Fast atom bombardment mass spectrometery represents an important mass spectral technique for the structure elucidation of complex natural products[9,10]. The FABMS methods provide molecular ions as well as their key fragments and thus generate useful structural information. These points will be illustrated from studies carried out in our laboratories on complex oligosaccharide antibiotics—everninomicins. The purpose of this report is to discuss the details of the technique which will be useful in

†Paper dedicated to Professor Ajay K Bose on the happy occasion of his sixtieth birthday.

future structural characterization of new members of such antibiotics.

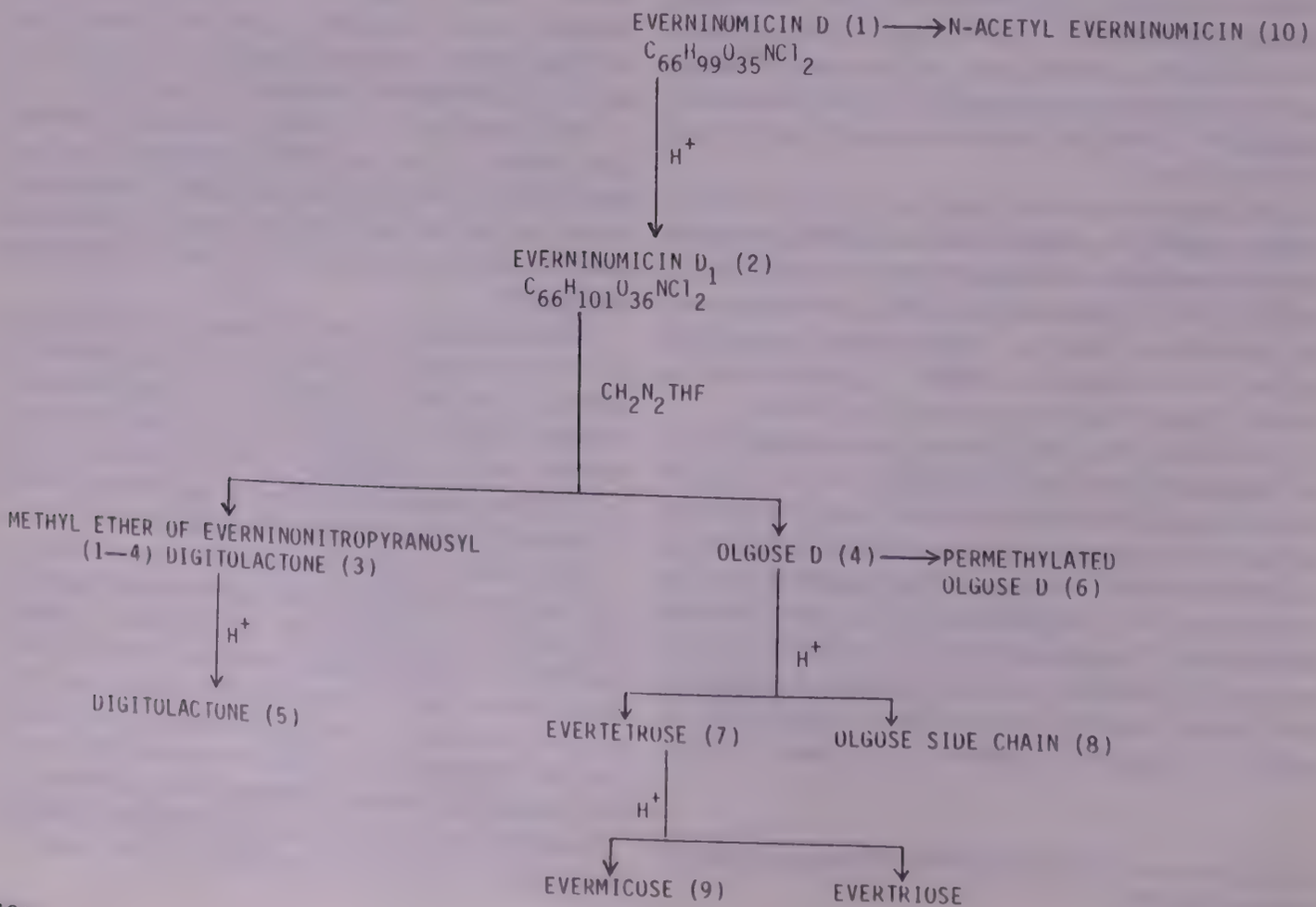
Everninomicins, a novel class of oligosaccharide antibiotics, are produced[11] by *Micromonospora carbonaceae*. They are highly active against gram-positive bacteria and Neisseria, including strains resistant to beta-lactams, macrolides, lincomycin, tetracycline and rifampicin. The antibiotic complex produced in the above fermentation consists of Everninomicin B, C and D. Everninomicin D (**1**) is the major component of the above complex. The structures and absolute stereochemistry of the above three antibiotics have been reported[12-14]. Everninomicins possess many unusual features in their structures such as the orthoester functionalities, an aliphatic methylene dioxy group, a nitro sugar and a fully substituted phenolic ester residue.

Everninomicins are essentially non-volatile and therefore they do not yield molecular ions in their mass spectra using electron impact (EI), chemical ionization (CI) and desorption chemical ionization (DCI) mass spectrometry.

Californium-252 plasma desorption technique displayed molecular ion of N-acetyleverninomicin D (**10**), however, the parent antibiotic everninomicin D (**1**) under similar conditions did not yield molecular ion. The above technique was of little value in obtaining fragment ions for structural information.

In our present investigation[15], we have used FABMS for determining the molecular weight of everninomicin D (**1**), the N-acetyl derivative (**10**) and its degradation products and to study their fragmentation patterns. High resolution FABMS data of important fragment ions were also obtained for structural information. We have noticed that the quality of the spectra depended on the solubility of the sample in the liquid[4] matrix with or without the aid of a cosolvent. The best results were obtained using glycerol-thioglycerol[3] mixture as a matrix and dimethyl sulfoxide as a solvent. Everninomicins and their degradation products showed pesudomolecular ion peaks $(M+H)^+$ and/or $(M+Na)^+$ of moderate intensity and also exhibited fragment ions which provided valuable structural information. Diethanolamine[15,16] (DEA) or triethanolamine (TEA) is a very useful matrix for the analysis of carbohydrates. Everninomicins provided intense adduct ions corresponding to $(M+TEAH)^+$ or $(M+DEAH)^+$ in their FAB mass spectra and limited fragment ions were displayed in most cases. A pseudomolecular ion peak

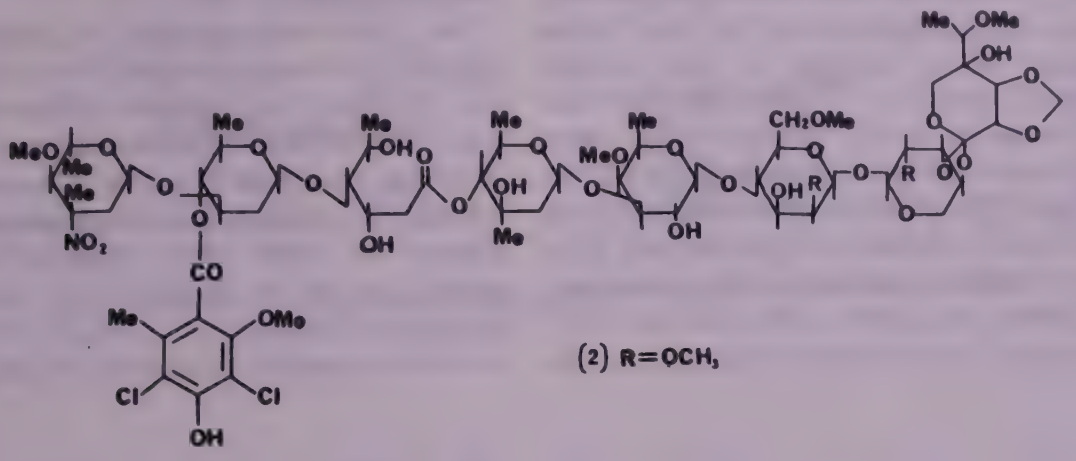
CHART 1



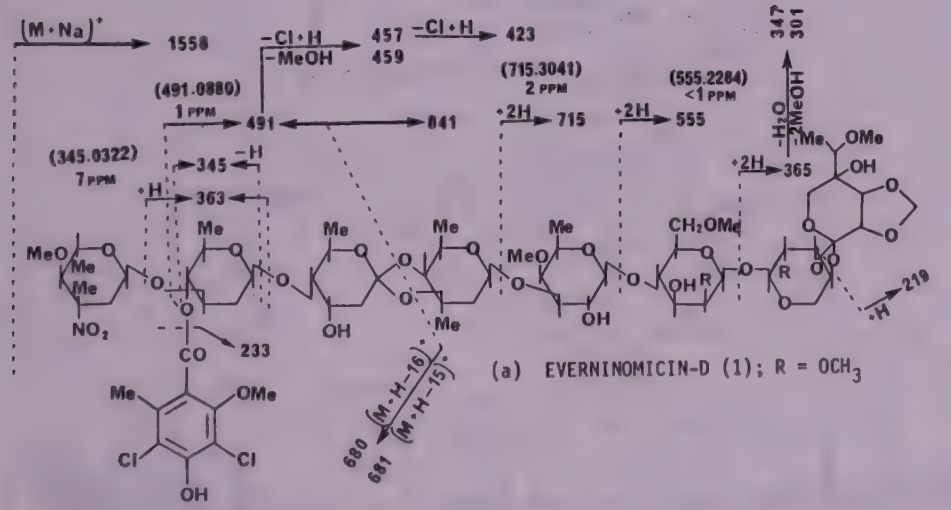
$(M+Na)^+$ of moderate intensity was also observed in the case of the parent antibiotics.

It has been disclosed during the structural elucidation of everninomicin D^{12-14} (**1**) in our laboratory that **1** on hydrolysis with aqueous acid yields everninomicin D_1 (**2**). On treatment with diazomethane, compound (**2**) undergoes cleavage to the lactone (**3**) and the olgose (**4**). These compounds were further converted into different derivatives by chemical derivatization and degradation (Chart 1). Information regarding the structures of compounds 3-9 were, therefore, of great consequences in the structural elucidation of **1**.

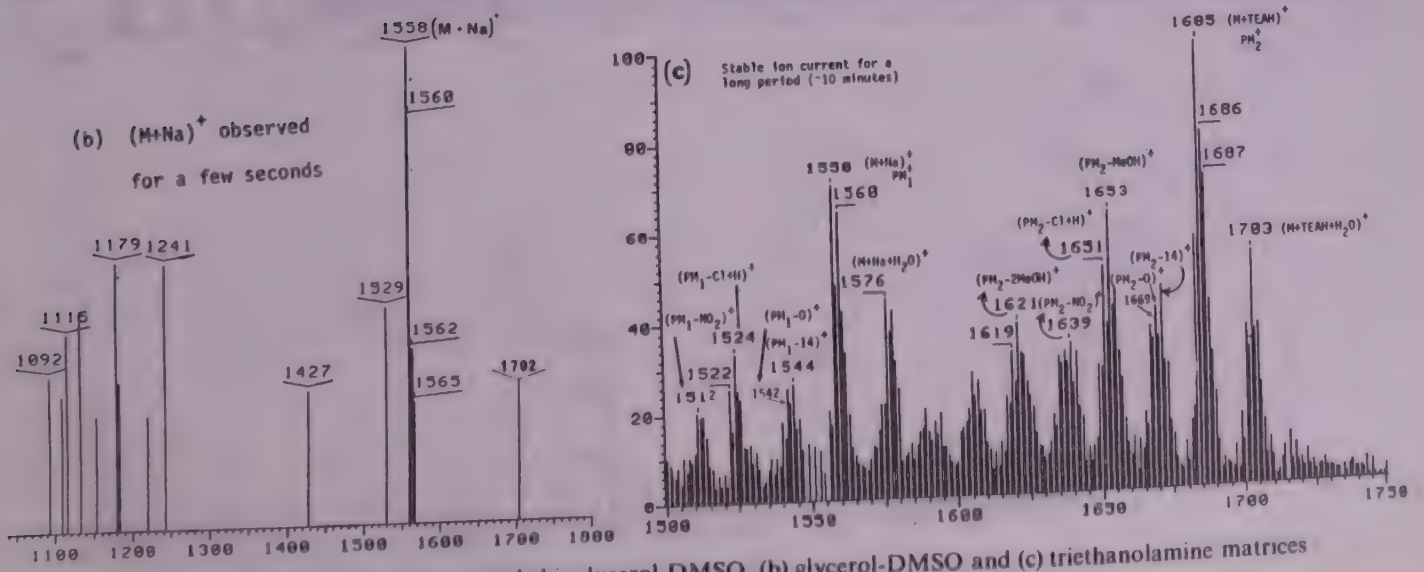
Figure 1 displays the FAB mass spectra of **1** in three different matrices. The FAB spectra in glycerol-thioglycerol-DMSO provided stable molecular ion as $(M+Na)^+$ at *m/z* 1558: adequate fragment ions were observed in the lower mass range of the spectrum (see Fig. 1a). A characteristic cleavage of the center orthoester provided two sets of ions which corresponded to the lactone (**3**) and the olgose D (**4**); additional fragment ions (*m/z* 680, 491, 363, 345, 233;



(2) R=OCH$_3$



(a) EVERNINOMICIN-D (1); R = OCH$_3$



(b) $(M+Na)^+$ observed for a few seconds

(c) Stable ion current for a long period (~10 minutes)

Fig. 1—FABMS of **1** in (a) glycerol-thioglycerol-DMSO, (b) glycerol-DMSO and (c) triethanolamine matrices

841, 715, 555, 365, 219) displayed in the spectra gave sequence information of each sugar unit. High resolution FABMS data were consistent with the structural assignment shown in Fig. 1a. We also noticed that fragment ions (*m/z* 457, 423) corresponding to the successive replacement of chlorine atoms by hydrogens are a characteristic of FAB-ionization method.

In Fig. 1b, the FAB mass spectrum of **1** in the high mass range (1000 to 1800 amu) using glycerol matrix is shown. The stability of the pseudomolecular ion $(M+Na)^+$ at *m/z* 1558 was very weak and appeared only in a few scans during acquisition of the data. Using triethanolamine as a matrix, a very strong pseudomolecular ion at *m/z* 1685 $(M+TEAH)^+$ and moderately intense ion at *m/z* 1558 $(M+Na)^+$ were observed in the spectra (Fig. 1c). A stable ion current in the mass range of 100 to 2000 amu was obtained for a long period of time (~10 min). The presence of a nitro group in the molecule was indicated by the appearance of fragment ions at *m/z* 1669, 1639, 1542 and 1512 which corresponded to the loss of oxygen and a nitro function from the pseudomolecular ions (For further details of these fragmentations, see Fig. 1c).

In Figs 2 and 3, FAB mass spectra of digitolactone (**5**) and its methyl ether (**3**) in three different matrices have been compared. Diethanolamine or triethanolamine is the best matrix for the determination of molecular weights of these classes of nitro sugars as they provide very intense pseudomolecular ions $(M+DEAH)^+$ or $(M+TEAH)^+$ in their mass spectra (Figs 2c and 3c); but limited structural information was forthcoming from these spectral data due to the lack of adequate fragment ions.

The FAB mass spectra in glycerol-thioglycerol mixture as a matrix provided very stable molecular ions $(M+Na)^+$ and valuable structural information were obtained from extensive fragment ions displayed in the spectra in Figs 2a and 3a. Glycerol matrix is not suitable in obtaining information on molecular weights of such nitro sugars; but structural information can be obtained from the fragment ions displayed in the spectrum in Fig. 2b. It is important to note that successive replacement of chlorine atoms by

Fig. 2—FABMS of **5** in (a) glycerol-thioglycerol-DMSO, (b) glycerol-DMSO and (c) diethanolamine matrices

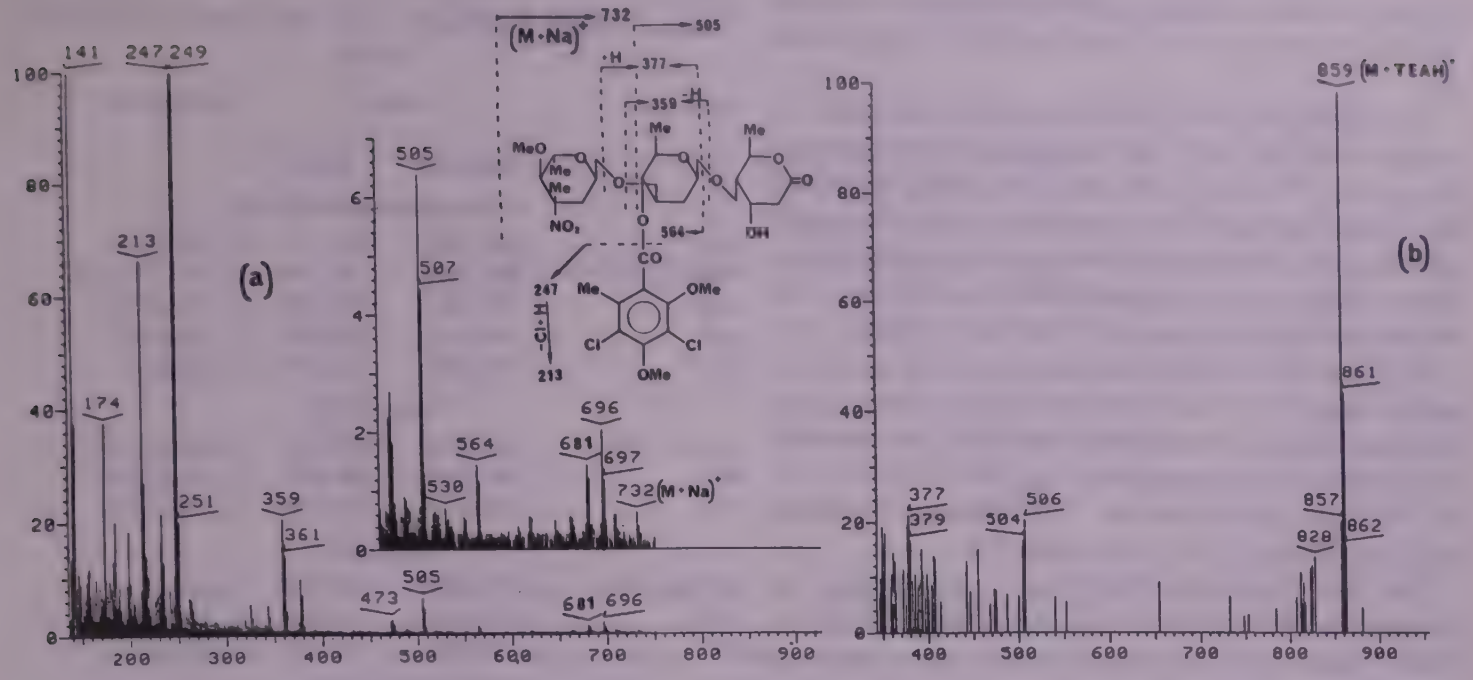


Fig. 3—FABMS of **3** in (a) glycerol-thioglycerol-DMSO and (b) triethanolamine matrices

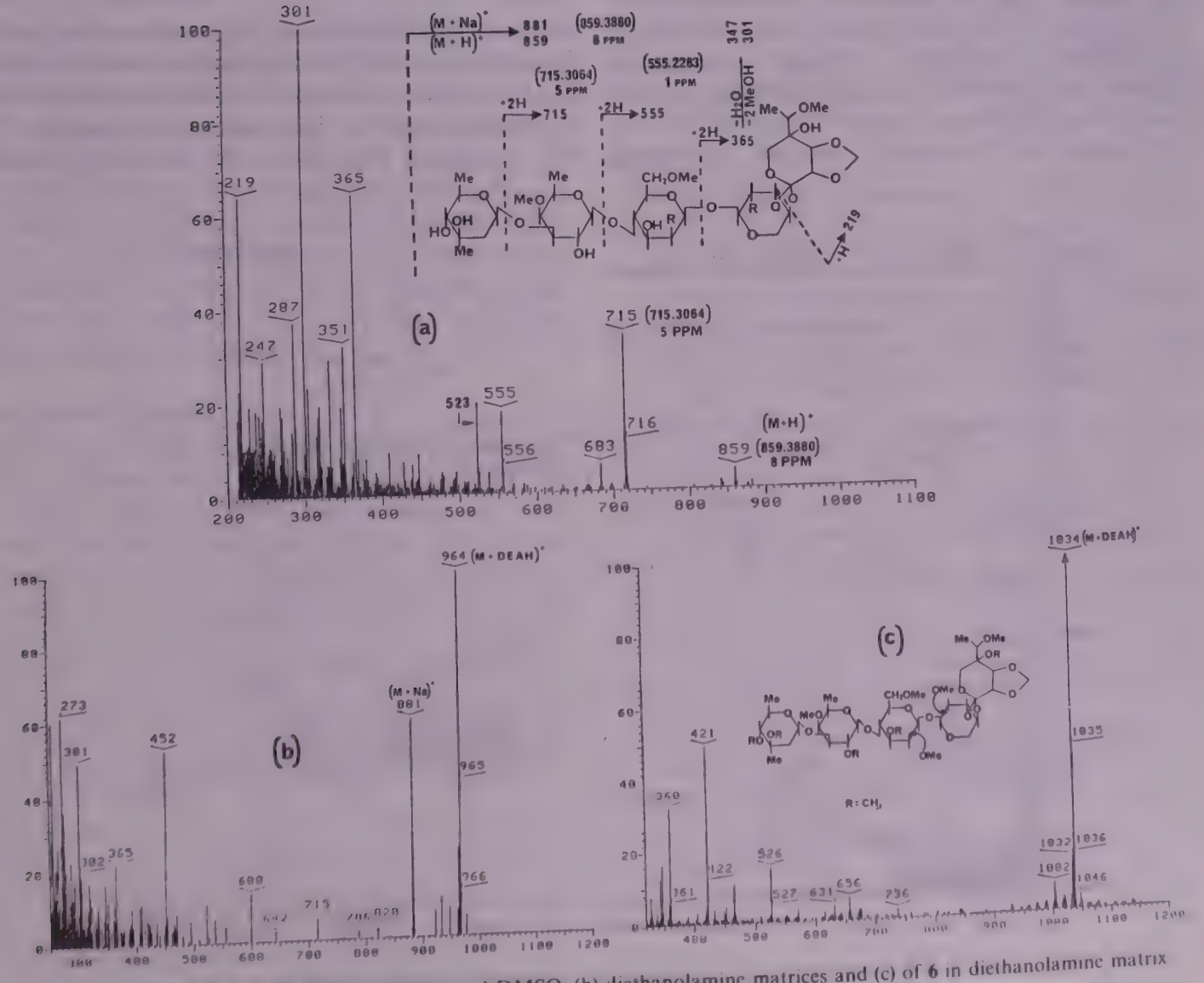


Fig. 4—FABMS of **4** in (a) glycerol-thioglycerol-DMSO, (b) diethanolamine matrices and (c) of **6** in diethanolamine matrix

hydrogens has also been noticed from these FABMS data (for example *m/z* 681, 647 and 613 - Figs. 2a and 2b).

The FAB spectrum of the olgose D (**4**) exhibited an ion at *m/z* 859 $(M+H)^+$ and contained major fragment ions at *m/z* 715, 555, 365 and 219 arising from the successive cleavage of the glycosidic bonds; structural information of each sugar moiety in sequential order was available from such spectral data (see Fig. 4a). The pseudomolecular ion peaks *m/z* 964 $(M+DEAH)^+$/*m/z* 881 $(M+Na)^+$ were the predominant ions when the sample was rerun in a diethanolamine matrix; the corresponding permethylated compound (**6**) showed predominant pseudomolecular ion $(M+DEAH)^+$ at *m/z* 1034 (see Figs 4b and 4c). A satisfactory FABMS data was obtained for compounds **7-9**.

The high resolution FAB mass spectral data of compounds **10**, **3**, **4** and **5** are summarized in Table 1. These data are consistent with the spectral interpretation discussed above.

As a test compound, we applied FAB technique for the structural studies of N-acetyleverninomicin (**10**) which is a potent antibiotic prepared from (**1**). The FAB mass spectrum of **10** displayed molecular ion $(M+Na)^+$ at *m/z* 1570 and provided two sets of ions by the cleavage of the center orthoester. One set of fragment ions characterized by the presence of two chlorine isotopes afforded structural features for part a; the other set of fragment ions free of chlorine isotopes, are consistent with the fragmentation pattern described in Fig. 5. The fragment ions at *m/z* 674, 457 and 423 appeared as a result of successive replacement of chlorine atoms by hydrogens in the spectra. The high resolution data at *m/z* 841 and 708 provided

Table 1—High Resolution FAB-MS Data of Evernino-micins

m/z	Mass		Composition
	Measured	Calc	
	N-Acetyleverninomicin (**10**)		
841	841.3746	841.3705	$C_{37}H_{61}O_{21}$
708	708.2243	708.2189	$C_{31}H_{44}NO_{13}Cl_2$
491	491.0887	491.0875	$C_{21}H_{25}O_9Cl_2$
345	345.0312	345.0296	$C_{15}H_{15}O_5Cl_2$
365	365.1461	365.1447	$C_{15}H_{25}O_{10}$
	Lactone (**5**)		
696 $(M+H)^+$	696.1868	696.1825	$C_{29}H_{40}O_{14}NCl_2$
491	491.0880	491.0875	$C_{21}H_{25}O_9Cl_2$
345	345.0322	345.0296	$C_{15}H_{15}O_5Cl_2$
	Olgose (**4**)		
859 $(M+H)^+$	859.3880	859.3810	$C_{37}H_{63}O_{22}$
715	715.3064	715.3024	$C_{30}H_{51}O_{19}$
555	555.2283	555.2288	$C_{23}H_{39}O_{15}$
	Lactone (**3**)		
710 $(M+H)^+$	710.2049	710.1981	$C_{30}H_{42}O_{14}NCl_2$
505	505.1069	505.1032	$C_{22}H_{27}O_9Cl_2$
359	359.0471	359.0452	$C_{16}H_{17}O_5Cl_2$

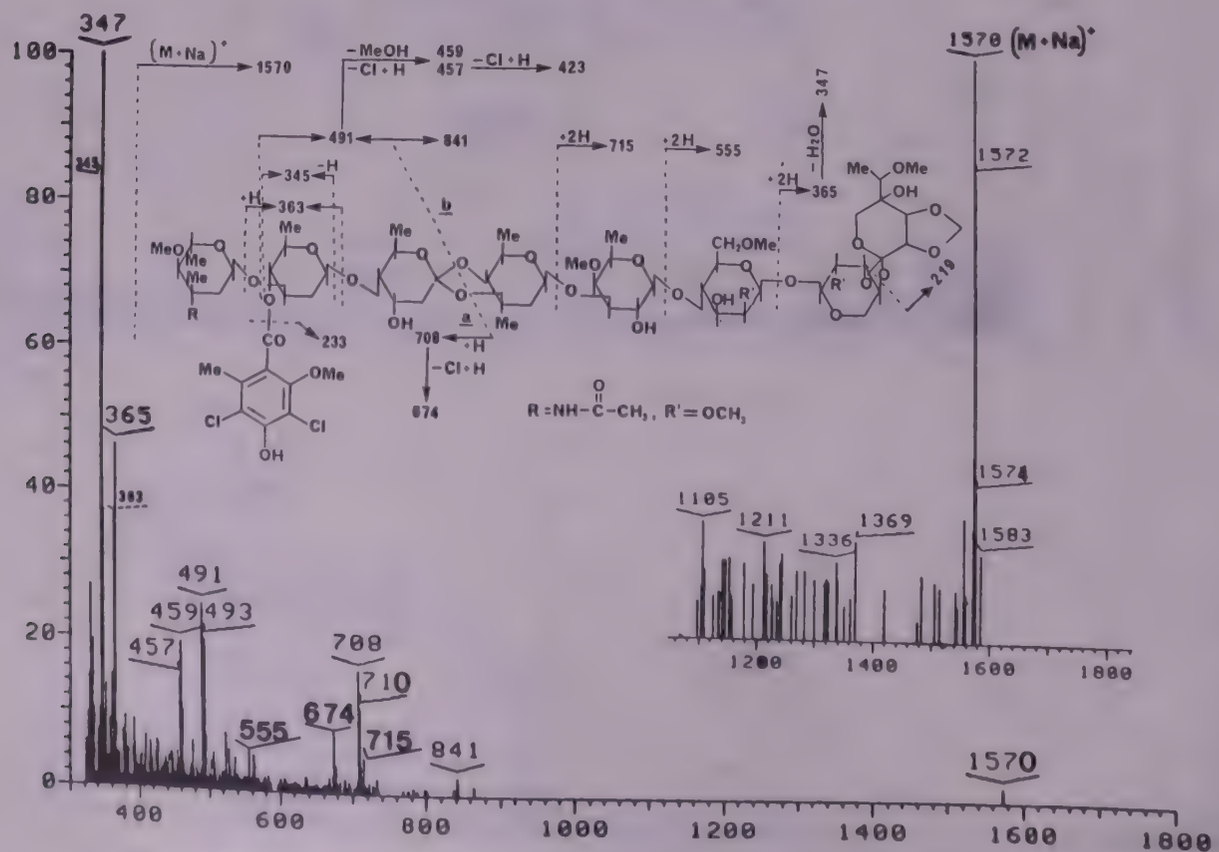
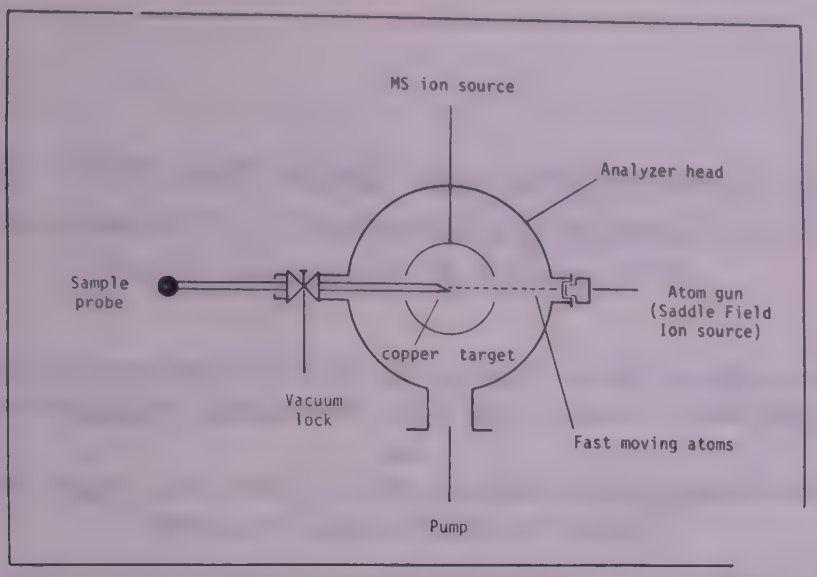


Fig. 5 FAB mass spectrum of N-acetyleverninomicin (**10**) in glycerol-thioglycerol matrix



Scheme 1—Overall diagram of FAB system (operation parameters: (a) energy of Xe atoms = 6-8 keV; (b) acceleration voltage = 3 kV (1 to 1400 amn) and 2 kV (1 to 2000 anm); (c) source temp. = 30°C; (d) analyzer head pressure = 2×10^{-5} torr; and (e) MS resolution = 1000 to 5000 (10% valley)

elemental composition of the molecule (**10**). A sample concentration of 1-5 μg/1 μl of DMSO in glycerol-thioglycerol mixture as a matrix provided satisfactory FAB mass spectra. The ion stability and sensitivity were satisfactory to permit high resolution measurement of ion peaks of interest by peak matching.

In conclusion, the FAB technique described above is a valuable approach for the structural elucidation of complex iligosaccharide antibiotics. We demonstrated the potential of this method for the structural studies of everninomicin-D (**1**), its derivatives and their chemical degradation products.

Experimental Procedure

A Finnigan MAT 312 mass spectrometer equipped with a CI/EI ion source was used (Finnigan MAT 312 is a high resolution mass spectrometer of Nier-Johnson geometry followed by an electrostatic analyzer). The atom gun, a saddle field ion source from Ion Tech Ltd, was mounted in place of one of the vacuum locks connected to the analyzer head. The probe with copper target on which sample were to be deposited was introduced into the ion source through the remaining vacuum lock on the left side of the analyzer head. The overall diagram of FAB system is shown in Scheme 1.

Samples were dissolved in DMSO (1-5 μg/ml) and deposited on the copper probe tip. A thin layer of glycerol-thioglycerol mixture (1:1) was applied to the probe tip containing the samples and mixed thoroughly with a pasteur pipet before insertion into the source. Diethanolamine (DEA) or triethanolamine (TEA) was also used as a matrix in place of glycerol-thioglycerol mixture for recording the FAB spectra. A homogeneous solution of samples in the matrix provided good FABMS data.

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Synthetic Studies in Diterpene Series: Part XII†—Synthesis of (±)-14-Ethyl-13-methylpodocarpa-8,11,13-triene—A Precursor of Veadeirol & Veadeiroic Acid

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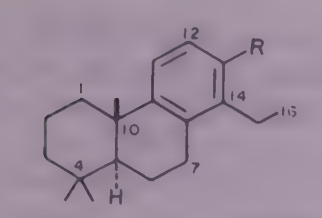
(±)-14-Ethyl-13-methylpodocarpa-8,11,13-triene (**7**) has been synthesised with a view to converting it into veadeirol (**1**) and veadeiroic acid (**2**), the two novel diterpenes having the rare cleistanthol skeleton. The key intermediate in the synthesis is 2-ethyl-3-methylbenzaldehyde (**15**) which in turn has been prepared from the oxime of 2-ethyl-3-methyl-cyclohex-2-onene, via a series of reactions. This aldehyde (**15**) is condensed with 3-methylbutan-2-one and the resultant styryl ketone (**16**) is converted into 2,4,4-trimethyl-3-styrylcyclohex-2-enone (**17**) by ring homologation. The latter on catalytic reduction over Pd/C (10%) followed by LAH reduction gives the substituted cyclohexanol (**19**) which on cyclialkylation with methanesulphonic acid and phosphorus pentoxide furnishes the desired 14-ethyl-13-methylpodocarpatriene (**7**). The cyclisation, however, is not stereoselective but gives appreciable amount of the *cis*-isomer. A preliminary attempt to convert the podocarpatriene (**7**) into veadeirol (**1**) and veadeiroic acid (**2**) through preferential functionalisation of the 13-methyl group has failed in the final step.

Recently, we have reported[1,2] the total synthesis of two naphthalenic norditerpenes (**5**) and (**6**) isolated from *Vellozia stipitata* and *V.declinans* by Brazilian workers[3], who in addition isolated two other diterpenoids, veadeirol (**1**) and veadeiroic acid (**2**) from the stem of *V. flavicans*[4]. The interest in these natural products lies in the fact that they contain the unusual skeleton of cleistanthol (**3**), isolated from the heartwood of *Cleistanthus schlecteri* along with a number of anti-isopimara-8(14)-diene derivatives, e.g. the 12-keto-compound (**4**)[5]. The last named compound acts as the biogenetic precursor of cleistanthol which is formed by migration of the vinyl group followed by aromatisation of ring-C. A further aromatisation of ring-B with the loss of 10-methyl group and formation of an ether linkage between C-7 and C-16 gives **5**; the 1,2-dehydro derivative (**6**) is possibly an artifact. In the present paper, we report a synthesis of (±)-14-ethyl-13-methylpodocarpa-8,11,13-triene (**7**), a possible precursor for **1** and **2**. Our preliminary attempt to convert this compound into **1** and **2** by preferential functionalisationn of the 13-methyl group, however, failed in the final step.

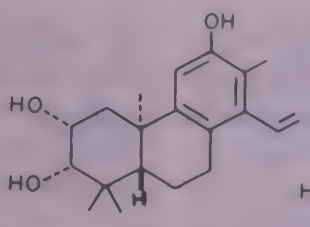
Several methods are available for the synthesis of podocarpa-8,11,13-triene system but none of them is wholly stereoselective. Recently, Davis *et al.*[6], have reported that 2-(2-arylethyl)-1,3,3-trimethylcyclohexyl cation (e.g., **23**) or its equivalent (**19**) undergoes cyclisation in the presence of a mixture of methanesulphonic acid and phosphorus pentoxide to afford *trans*-podocarpatriene exclusively. We, therefore, decided to adopt an earlier method of Ireland *et al.*[7] (also used in our laboratory[8,9]) which affords substrates of the type (**19**) in a straightforward manner. The key intermediate for the synthesis is 2-ethyl-3-methylbenzaldehyde (**15**). It was thought that 2-ethyl-3-methylcyclohex-2-enone (**9**) would be an appropriate starting material for a large scale preparation of **15** via a sequence of reactions summarized in Scheme 1. However, our attempts to prepare **9** by path (A) or (B) proved unsatisfactory. Alkylation of ethyl cyanoacetate with *n*-propylmagnesium bromide did not give any appreciable yield of ethyl 3-oxohexanoate (**8**) although the reaction went very well with ethylmagnesium iodide to yield the lower homologue of the β-oxoester[10]. In the second method, the ethylation of cyclohexane-1,3-dione proved unrewarding.

Finally, ethyl 2-methylcyclohex-2-en-4-one-1-carboxylate (Hagemann's ester) was alkylated with ethyl iodide (Scheme 2). In conformity with our earlier observations[11,12], ethylation of Hagemann's ester led to a mixture of 3-methyl-(**10**) and 1-ethyl-(**11**) derivatives in an approximate ratio of 80:20. Preferential hydrolysis of the less hindered derivative **10**[13] and subsequent separation of **9** from the keto-ester (**11**) did not work in this case. The mixture of ketones on alkaline hydrolysis contained slightly more than 80% of the desired **9** which could not be separated

† For Part XI, see Nasipuri D, Mahapatra B & Das G, in *J Indian Chem Soc*, (In press).



(1), R = CH_2OH
(2), R = CO_2H



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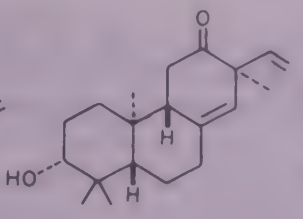

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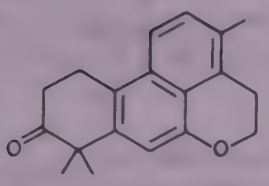

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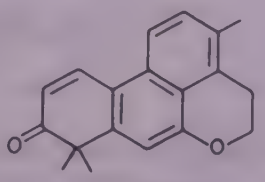

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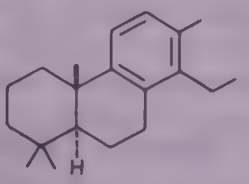

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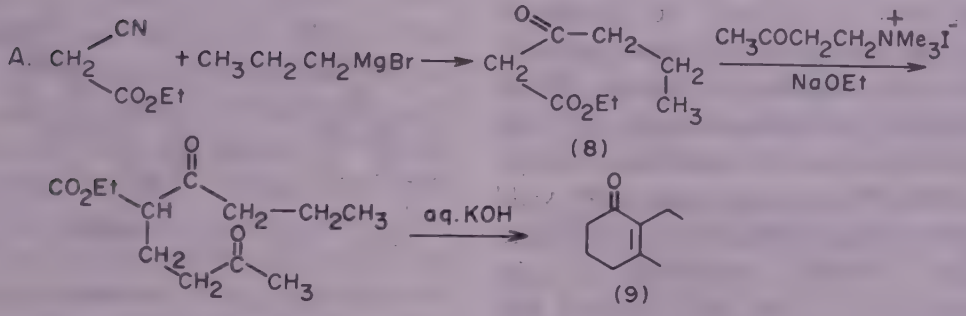
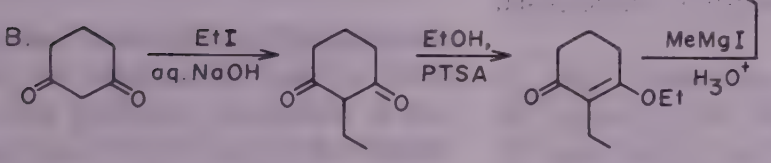
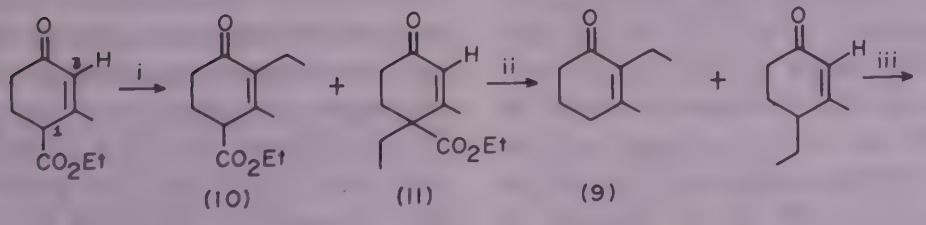
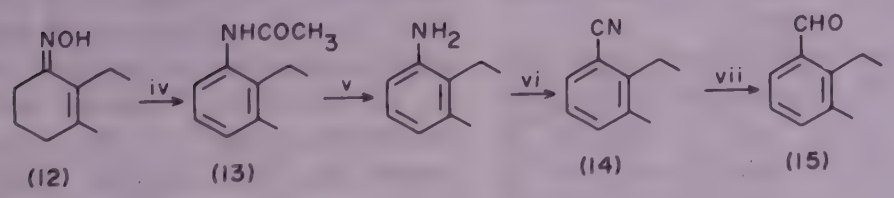




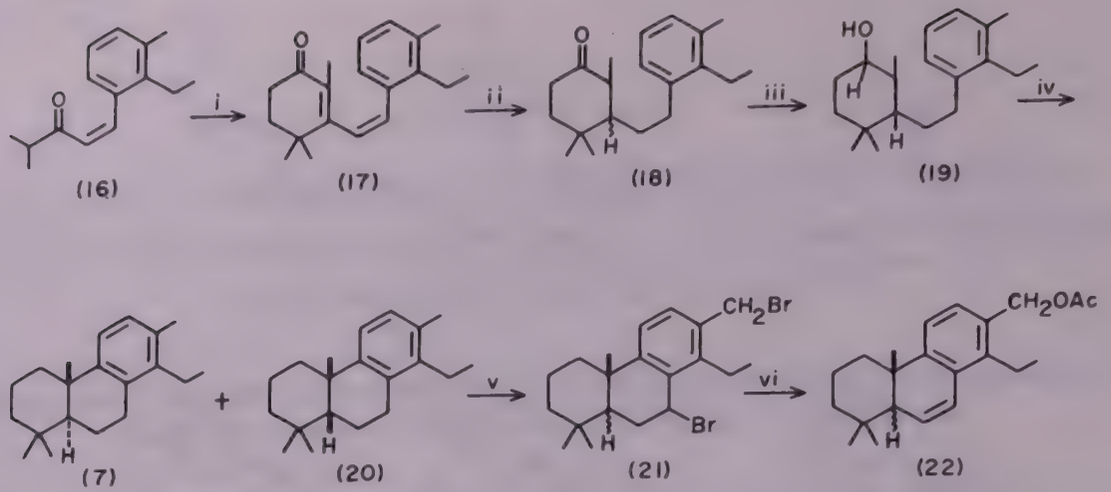
Scheme 1





Scheme 2. Reagents : i ; NaOEt, EtI, EtOH. ii ; KOH, EtOH, H_2O and heat. iii ; NH_2OH, Py. iv ; Ac_2O, Py, AcCl and heat. v ; HCl. vi ; $NaNO_2$, HCl, $Cu_2(CN)_2$. vii ; $LiAl(OEt)_3H$.

from the 4-ethyl-3-methylcyclohexenone. Oximation of the mixture followed by recrystallisation, however, afforded a single oxime (**12**). Lack of any vinyl proton in its PMR spectrum confirmed the complete absence of the other isomer. The purified oxime was then submitted to Semmler-Wolff aromatisation reaction[14,15] to give the substituted acetanilide (**13**) as a crystalline solid in an overall yield

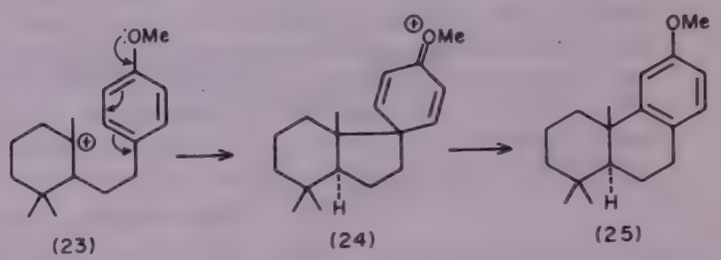


Scheme 3. Reagents: i; $MeCH_2COCH_2CH_2\overset{+}{N}Et_2$ Me I^-, KOEt. ii; Pd-C (10%), H_2. iii; $LiAlH_4$ in Et_2O. iv; $MeSO_3H$-P_2O_5. v; N-Bromosuccinimide in CCl_4. vi; NaOAc and heat.

of ~40%. This was hydrolysed to 2-ethyl-3-methylaniline and the latter converted into 2-ethyl-3-methylbenzonitrile (**14**) by Sandmeyer reaction. All the compounds were found to be homogeneous by GC and PMR. The nitrile (**14**) was next converted into 2-ethyl-3-methylbenzaldehyde (**15**) in a single step in 80% yield by reducing **14** with an equivalent amount of lithium triethoxyaluminium hydride according to the procedure of Brown *et al.*[16] (see also Nasipuri and Pyne[17]). The benzaldehyde (**15**) was fully characterised by PMR spectrum.

The aldehyde (**15**) was condensed with 3-methylbutan-2-one to furnish the styryl ketone (**16**) (Scheme 3) almost in quantitative yield. Reaction of **16** with the methiodide of 1-N-diethylaminopentan-3-one[9] in the presence of potassium ethoxide led to 2,4,4-trimethyl-3-styrylcyclohex-2-enone (**17**) in excellent yield. The two double bonds in the ketone were smoothly reduced by catalytic hydrogenation and the saturated ketone (**18**) was further reduced with an ethereal solution of lithium aluminium hydride to afford the cyclohexanol (**19**) as a mixture of diastereoisomers. One major and two minor peaks were visible in GC (FFAP column).

The alcohol (**19**) was cyclialkylated under two conditions: (i) heating with polyphosphoric acid at 90° for 1 hr[9] and (ii) treating with a mixture of methanesulphonic acid and phosphorus pentoxide[6] at 25° for 15 min. In both the cases, gas chromatographic analysis indicated the presence of only two products in identical ratio; the *trans*-podocarpatriene (**7**) to the extent of 55-60% and the *cis*-isomer (**20**) to the extent of 40-45%. The identity of the two components was confirmed by GC-MS and PMR spectrum of the mixture. Moreover, the two isomers were separated by preparative TLC and each of the components was examined by PMR. The *cis*-isomer (**20**) was



Scheme 4

characterised by a high field methyl signal at δ 0.39 (4-β-Me) shielded by aromatic ring current[18] and there was no ambiguity regarding the identity of the two compounds (see ref. 19 for other possible products of cyclisation). It appears, therefore, that the observation of Davis *et al.*[6] that cyclisation leads exclusively to the *trans*-podocarpatriene is based on insufficient data (only one substrate was cyclised). It is possible that the mechanism of cyclisation of that particular substrate (**23**) (see Scheme 4) with a *p*-methoxyphenethyl side chain may be different and possibly goes through a spiro-intermediate (**24**) (with A/B rings *trans*) which subsequently rearranges to the podocarpatriene (**25**). This type of cyclisation with more or less similar substrates has been carried out by many workers either for the synthesis of natural products[20-22] or for mechanistic study[23-24]. But in no case, pure *trans*-isomer has been isolated. Further study on the mechanism of this cyclisation vis-a-vis its stereochemistry is necessary and experiments in this direction are in progress in our laboratory.

A stereoisomeric mixture of the 14-ethyl-13-methylpodocarpatriene containing 60% of the *trans*-isomer was brominated with N-bromosuccinimide[25] with the hope that bromination would take place preferentially at 13-methyl. The crude product was converted into the acetate directly by heating with

potassium acetate. The product was identified as the 6,7-dehydroveadeiryl acetate (**22**) admixed with some *cis*-isomer (~15%). Evidently, bromination took place simultaneously at the methyl side chain as well at C-7 to give the dibromo compound (**21**) and during heating with acetate the bromine at C-7 underwent dehydrobromination. The product was analysed by PMR and mass spectra. In view of the product being a mixture of *cis*- and *trans*-isomer, no attempt was made to reduce it catalytically. An alternative synthetic approach to veadeirol **1** and veadeiroic acid (**2**) is being contemplated.

Experimental Procedure

All melting and boiling points are uncorrected. Melting points were taken in open capillaries in sulphuric acid bath. IR spectra (ν_{max} in cm^{-1}) were recorded on a Perkin-Elmer infracord spectrophotometer, model 237B, PMR spectra (δ ppm) on a Varian EM 390 90 MHz machine in $CDCl_3$ using TMS as an internal standard and mass spectra on a Hitachi RMU-GL spectrometer at 75 eV using direct inlet system. The GC-MS experiments were carried out by one of us (A K S) at the Tokyo Institute of Technology, Tokyo, Japan. Homogeneity of the compounds was checked by TLC on silica-gel using iodine vapour as visualising agent. Gas chromatography was done on a Varian 3700 gas chromatograph using FFAP (15%), SE 30 (10%) and carbowax (15%) columns. Petroleum refers to a fraction, b.p. 40-60°. All organic solutions were dried over anhydrous sodium sulphate.

Ethylation of ethyl 2-methylcyclohex-2-en-4-one-1-carboxylate (Hagemann's ester)

Ethylation of Hagemann's ester with ethyl iodide in the presence of sodium ethoxide was carried out following the producure of Sarkar and Nasipuri[26]. A mixture of ethyl 3-ethyl-2-methylcyclohex-2-en-4-one-1-carboxylate (**10**) and ethyl 1-ethyl-2-methylcyclohex-2-en-4-one-1-carboxylate (**11**) was obtained with the former predominating (75-80%), b.p. 117-20°/0.2 mm.

2-Ethyl-3-methylcyclohex-2-enone (**9**) *and 4-ethyl-3-methylcyclohex-2-enone*

The foregoing mixture (58.5 g, 0.28 mol) was heated under reflux with ethanolic 15% potassium hydroxide (160 ml) for 9 hr. Most of the solvent was distilled off and the residue diluted with water. The aqueous solution was acidified with hydrochloric acid and the mixture heated at 80° for 1 hr to complete decarboxylation. The organic matter was taken up in ether and the product distilled using an efficient fractionating column to furnish the mixture of cyclohexenones (25.5 g, 66%), b.p. 75-78°/0.8 mm. GC analysis showed it to be a mixture of two ketones, 2-methylcyclohex-2-enone (**9**) (85%) and 4-ethyl-3-methylcyclohex-2-enone (15%). The PMR spectrum of the mixture had the vinylic proton at δ 5.77 (s) accounting for 0.15 proton thus confirming the results of GC analysis.

Oxime (**12**) *of 2-ethyl-3-methylcyclohex-2-enone* (**9**)

The above mixture of ketones (22 g) was mixed with hydroxylamine hydrochloride (12 g), pyridine (13.5 ml), and sufficient methanol to effect complete dissolution and allowed to stand for 24hr. The precipitated crystalline solid was filtered to give **12** (18g, 75%), m.p. 100°, which recrystallised from methanol in long needles (15 g), m.p. 104° (Found: C, 70.6; H, 9.8; N, 9.1. $C_9H_{15}NO$ requires C, 70.6; H, 9.8; N, 9.15%); PMR: 9.00 (*s*, 1H, =NOH), 2.60 (*q*, 2H, J=7 Hz, CH_2CH_3), 2.33 (*t*, 2H, J=7 Hz, 4-H_2), 2.15 (*t*, 2H, J =7 Hz, 6-H_2), 1.85 (*s*, 3H, 3-CH_3), 1.70 (*t*, J=7 Hz, 5-H_2) and 1.03 (*t*, 3H, J=7 Hz, CH_2CH_3).

2-Ethyl-3-methylacetanilide (**13**)

A solution of **12** (22 g) in acetic anhydride (100 ml) and pyridine (12ml) was refluxed for 1hr and then cooled. Acetyl chloride (30ml) was added and the mixture refluxed for a further period of 30 min. Hydrolysis and neutralisation with ammonium hydroxide gave a precipitate which was collected, dried and crystallised, from benzene to afford **13**(12.6 g, 50%), m.p. 140-42° as silky needles (Found: C, 74.5; H, 8.5; N, 8.1. $C_{11}H_{15}NO$ requires C, 74.6; H, 8.5; N, 7.9%); PMR: 7.12 (*m*, 3H, ArH), 2.60 (*q*, 2H, J=7 Hz, CH_2CH_3), 2.37 (*s*, 3H, 3-CH_3), 2.17 (*s*, 3H, $COCH_3$), 2.00 (*s*, 1H, NH), 1.10 (*t*, 3H, J=7 Hz, CH_2CH_3).

2-Ethyl-3-methylaniline

A suspension of **13** (12.1 g) in hydrochloric acid (1 : 1) was refluxed for 3 hr and cooled to give light yellow-coloured needles of the hydrochloride of 2-ethyl-3-methylaniline. This was dissolved in water, any neutral matter present extracted with chloroform and the aqueous solution basified with dil alkali to liberate the free aniline. This was extracted with ether, dried and the solvent removed. The residue on distillation afforded 2-ethyl-3-methylaniline (7.3 g, 80%), b.p. 95-98°/5 mm (Found: C, 80.1; H, 9.65. $C_9H_{13}N$ requires C, 80.0; H, 9.6%).

2-Ethyl-3-methylbenzo-nitrile (**14**)

A solution of the above aniline (7.2 g) in conc hydrochloric acid (15 ml) and cold water (50 ml) was cooled to 0° and diazotised with a solution of sodium nitrite (3.75 g) in water (5 ml). The final volume of the

solution was made up to 70 ml and the solution cautiously neutralised by adding solid sodium carbonate with constant stirring. Meanwhile, a solution of cuprous cyanide was prepared from copper sulphate (18.75 g) by first converting it into cuprous chloride and then adding sodium cyanide (9.5g). The mixture was chilled to 0→ and benzene (50ml) was poured on the surface. To it, the diazotised solution was added slowly and the mixture was stirred for 3 hr when it attained the room temperature. The upper benzene layer was separated and subjected to steam-distillation, The distillate was extracted with ether, dried, solvent removed and the residue distilled to afford **14** (3.1 g, 41%), b.p. 85°/2 mm (Found: C, 82.7; H, 7.6. $C_{10}H_{11}N$ requires C, 82.8; H, 7.6%); IR ($CHCl_3$): 2210; PMR: 7.60-7.10 (*m*, 3H, ArH), 2.90 (*q*, 2H, $J=7$ Hz, 2-CH_2), 2.13 (*s*, 3H, 3-CH_3) and 1.20 (*t*, 3H, $J=7$ Hz, $-CH_2CH_3$).

2-Ethyl-3-methylbenzaldehyde (**15**)

Absolute ethanol (2.86 g, 0.0621 mol) was added to a stirred solution (30 ml, 0.69 mol) of lithium aluminium hydride (0.0207 mol) in dry ether. It was cooled in an ice-bath and **14** (3 g, 0.020 mol) in dry ether (10 ml) was added all at once with vigorous stirring. The stirring was continued for 1 hr more, the reaction mixture cooled and hydrolysed with 5*M* cold sulphuric acid (20 ml). The ether layer was separated, the aqueous layer extracted once with ether and the total extract dried. The residue after removal of ether was distilled to furnish **15** (2.25 g, 85%), b.p. 92°/12 mm (Found: C, 81.15; H, 8.2. $C_{10}H_{12}O$ requires C, 81.1; H, 8.1%); IR: 1680; PMR: 10.40 (*s*, 1H, −CHO); 7.80 (*dd*, 1H, $J=8$ and 2 Hz, 6-H), 7.60-7.20 (*m*, 2H, ArH), 3.10 (*q*, 2H, $J=7$ Hz, 2-CH_2), 2.40 (*s*, 3H, 3-CH_3) and 1.20 (*t*, 3H, $J=7$ Hz, 2-CH_2CH_3).

1-(2′-Ethyl-3′-methylphenyl)-4-methylpent-1-en-3-one (**16**)

The aldehyde **15** (4.4 g, 0.03 mol) was mixed with isopropyl methyl ketone (1.3 g, 0.03 mol) and to the mixture, ethanol (12 ml) and aq. 5% sodium hydroxide (6 ml) were added. The mixture was shaken for 10 hr, extracted with ether, the ethereal extract washed with water, dried and the solvent evaporated. The residue was distilled to give **16** (4.0 g, 63%), as a viscous gum, b.p. 142-44 /12 mm (Found: C, 83.4; H, 9.2. $C_{15}H_{20}O$ requires C, 83.3; H, 9.3%); IR: 1680; PMR: 8.10 (*d*, 1H, $J=15$ Hz, 1-H), 7.53 (*dd*, 1H, $J=8$ & 2 Hz, 6′-H), 7.40-7.20 (*m*, 2H, ArH), 6.78 (*d*, 1H, $J=15$ Hz, 2-H), 2.80 (*m*, 3H, 2′-CH_2 + 4-H), 2.37 (*s*, 3H, 3′-CH_3), and 1.20 (*m*, 9H, $3\times CH_3$).

2,4,4-Trimethyl-3-(2′-ethyl-3′-methylstyryl)-cyclohex-2-en-1-one (**17**)

The methiodide[9] of 1-N-diethylaminopentan-3-one[9] was prepared by slow addition of methyl iodide (3.85g, 0.027 mol) at 0° to the base with stirring when a white solid formed. It was allowed to stand overnight at room temperature. Potassium ethoxide prepared from potassium (1.8 g) and dry ethanol (30 ml) was added slowly to a mixture of the above methoiodide and **16** (3.9 g) with vigorous shaking and the mixture heated under reflux for 8 hr. The solvent was removed at the water pump, the residue acidified with 2*N* sulphuric acid and the organic matter extracted with ether. After the removal of the solvent, the residue was distilled to afford **17** (3 g, 58%), b.p. 170-75°/0.5 mm (Found: C, 85.2; H, 9.2. $C_{20}H_{26}O$ requires C, 85.1; H, 9.2%; IR: 1670 PMR: 7.60 (*dd*, 1H, $J=8$ & 2 Hz, 6′-H), 7.30-7.20 (*m*, 2H, ArH), 6.97 (*d*, 1H, $J=15$ Hz, vinyl H), 6.63 (*d*, 1H, $J=15$ Hz, vinyl H), 2.73 (*q*, 2H, $J=7$ Hz, 2′-CH_2), 2.57 (*t*, 2H, $J=7$Hz, 6-H_2), 2.37 (*s*, 3H, 3′-CH_3); 1.96 (*s*, 3H, 2-CH_3), 1.92 (*m*, 2H, 5-H_2), 1.25 (*s*, 6H, 4-Me_2) and 1.13 (*t*, 3H, $J=7$ Hz).

2,4,4-Trimethyl-3-(2-ethyl-3-methylphenyl)-ethylcyclohexanone (**18**)

17 (3g, 0.0106 mol) was mixed with Pd/C (0.20 g, 10%) in ethanol (50 ml) and shaken in an atmosphere of hydrogen. After the uptake of theoretical amount of hydrogen (2 mol) (4 hr), the product was worked-up in the usual way to furnish **18** as an oil (2.6 g), b.p. 160-65°/0.5 mm (Found: C, 84.6; H, 10.5. $C_{20}H_{30}O$ requires C, 83.9; H, 10.5%); IR ($CHCl_3$): 1700; PMR: 7.17 (*s*, 3H, ArH), 2.65 (*m* 4H, $2\times CH_2$), 2.37 (*s*, 3H, ArCH_3), 2.37 (*t*, 2H, $J=7$ Hz, 6-H_2), 1.65 (*m*, 5H, $2\times CH_2 + CH$) and 1.30-1.00 (*m*, 12H, $4\times CH_3$).

2,4,4-Trimethyl-3-(2-ethyl-3-methylphenyl)-ethylcyclohexanol (**19**)

18 (2.5 g) was reduced with an excess of ethereal solution of lithium aluminium hydride and worked up in the usual way to afford **19**; IR ($CHCl_3$): 3500. It was directly used for the cyclisation experiments.

(±)-*13-Methyl-14-ethylpodocarpa-8-8,11,13-trienes* (**7**) *and* (**20**)

To freshly distilled methanesulphonic acid (100 g) was added in phosphorus pentoxide (10 g) in one portion and allowed to dissolve while stirring for 1-2 hr.

The above reagent (19.0 g) was added to **19** (0.25 g) and the mixture stirred at 25° for 15 min. It was decomposed with cold water and the organic matter extracted with ether (25 ml × 3). The ethereal extract was washed with 10% sodium hydroxide followed by

water, dried and the solvent evaporated. The residue was chromatographed over silica-gel to give a clear liquid (200 mg). The gas chromatographic analysis using FFAP, carbowax and SE 30 columns showed it to be a mixture of *trans*- (55%)- and *cis*-(45%)-podocarpatrienes. When cyclised with polyphosphoric acid at 90° for 1 hr, **19** gave almost an identical mixture.

A part of the above mixture of podocarpatrienes was separated by reverse phase preparative chromatography using methanol as eluent. (±)-13-Methyl-14-ethylpodocarpa-8,11,13-triene (**7**) (5 mg) and the corresponding *cis*-isomer (**20**) (3 mg) were isolated in this way. PMR of the *trans*-isomer (**7**) had the following peaks: 7.00 (*q*, 2H, $J=8$ Hz, ArH), 2.88 (*m*, 2H, 7-H_2), 2.64 (*q*, 2H, $J=7$ Hz, 14-CH_2), 2.28 (*s*, 3H, Ar-CH_3), 1.28 (*s*, 3H, 10-Me), 1.20 (*t*, 3H, $J=7$ Hz, $ArCH_2CH_3$); the rest of the protons appeared as broad peaks in the region 1.48-1.00 ($4\times CH_2+CH$). The *cis*-isomer (**20**) had the PMR peaks of 6.95 (*m*, 2H, ArH), 2.80 (*m*, 2H, 7-H_2), 2.56 (*q*, 2H, $J=7$ Hz, 14-CH_2), 1.24 (*s*, 3H, 10-Me), 1.14 (*t*, 3H, $J=7$ Hz, 14-CH_2CH_3), 0.92 (*s*, 3H, a-4-Me); the rest of the protons appeared as broad peaks in the region 1.48-1.00. The mass spectra of the two isomers were identical: *m/z*, 270 (M^+), 225, 185, 173, and 158 and others.

A sublimed sample was analysed (Found: C, 88.85; H, 11.1. $C_{20}H_{30}$ requires C, 88.9; H, 11.1%).

Bromination of podocarpatrienes: *Bromo derivatives* (**21**)

To a hot solution of the above mixture of *trans* (65%) and *cis* (45%) podocarpatrienes (300 mg) in carbon tetrachloride (60 ml) was added N-bromosuccinimide (0.178 g) and benzoyl peroxide (3 mg). The resulting solution was heated under reflux for 2 hr under nitrogen using tungsten-filament lamp. Succinimide separated out of the solution. It was filtered out and the organic matter was extracted with ether, the extract washed with water, dried and evaporated to give the crude brominated product (**21**).

Acetylation of the bromo-derivatives (**21**): *cis- and trans-6,7-dehydroveadeiryl acetate* (**22**)

The crude **21** (280 mg) was refluxed with powdered sodium acetate (600mg) and gl acetic acid (5ml) at 160-70° in an oil-bath for 10 hr. The acetic acid was removed by distillation and the residue treated with aq 10% sodium hydrogen carbonate and finally extracted with ether. The ethereal extract was washed with water, dried solvent removed and the residue chromatographed over silicagel to furnish a mixture which consisted mainly of the *cis*- and *trans*-isomers of **22**; PMR: 7.35-7.00 (*m*, 2H, ArH), 6.75 (*d*, 1H, $J=11$Hz, 7-H), 6.02 (*dd*, 1H, $J=11$ & 7 Hz, 6-H), 4.80 (*s*, 2H, 13-CH_2OAc), 2.85×2.72 ($2\times t$, 2H, $J=7$ Hz, 14-CH_2), 2.30 (*s*, 3H, $OCOCH_3$), 1.80-0.95 (*m*, 22H) and 0.26 (*s*, 0.15H, 4-β-Me).

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Steroids & Related Studies: Part 77—Certain Azaspirostans

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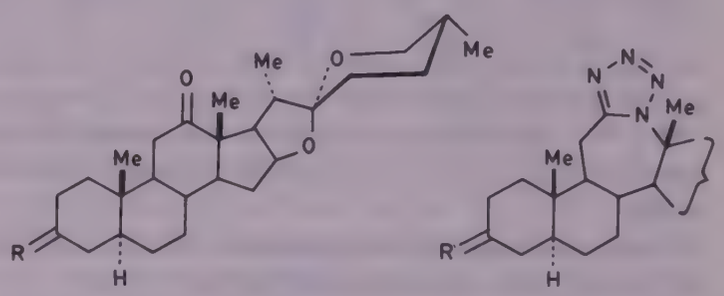
(25*R*)-5α-Spirostan-3,12-dione (**3**) on Schmidt reaction gives three products which are considered to have structures (25*R*)-3,12a-diaza-A,C-bishomo-5α-spirostano[3,4-*d*][12a,12-*d*]bistetrazole (**6**), (25*R*)-4,12a-diaza-A,C-bishomo-5α-spirostano[4,3-*d*][12a,12-*d*]bistetrazole (**7**) and (25*R*)-3,12a-diaza-A,C-bishomo-5α-spirostano[12a,12-*d*]tetrazol-4-one (**8**) or (25*R*)-4,12a-diaza-A,C-bishomo-5α-spirostano[12a,12-*d*]tetrazol-3-one (**9**). The products (**6**) and (**7**) are also obtainable on Schmidt reaction with (25*R*)-12a-aza-C-homo-5α-spirostano[12a,12-*d*]tetrazol-3-one (**5**). Oxime of the latter gives a product which may have structure (**8**) or (**9**). (25*R*)-12a-Aza-C-homo-5α-spirostan-3,12-dione (**10**) gives two tetrazoles of structures (25*R*)-3,12a-diaza-A,C-bishomo-5α-spirostano[3,4-*d*]tetrazol-12-one (**11**) and (25*R*)-4,12a-diaza-A,C-bishomo-5α-spirostano[4,3-*d*]tetrazol-12-one (**12**). 3,12-Dioxime of **3** or 3-oxime of **10** on Beckmann rearrangement gives a dilactam which may have structure (25*R*)-3,12a-diaza-A,C-bishomo-5α-spirostan-4,12-dione (**13**) or (25*R*)-4,12a-diaza-A,C-bishomo-5α-spirostan-3,12-dione (**14**).

The medicinal chemistry of tetrazoles is of interest[1]. In this laboratory extensive studies have been carried out on steroidal tetrazoles[2-8]. In this paper we describe the synthesis of azaspirostans and spirostan tetrazoles.

It had been noted that structures of tetrazoles fused to alicyclic systems can be determined by PMR spectroscopy[9]. The methylene protons next to nitrogen appear as a multiplet at δ 4.50 and those next to carbon of tetrazole appear as a multiplet near δ 3.00. In one of our earlier studies, hecogenin acetate (**1**) on Schmidt reaction yielded a tetrazole, which was assigned structure (**2**)[10]. It did not show a signal at δ 4.50 but a four-proton multiplet appeared at δ 3.20-3.75 assignable to 11-CH_2 and 26-CH_2 protons. The 18-methyl appeared as singlet at δ 1.42. We thought of carrying out Schmidt reaction with (25*R*)-5α-spirostan-3,12-dione (**3**). Such a reaction could lead to lactam and tetrazole systems and from **3** there was the possibility of getting no less than sixteen compounds. The results of this study are presented in this paper.

When **3** was treated with excess of hydrazoic acid in chloroform in the presence of boron trifluoride two bistetrazole products A (m.p. 330-32°) and B (m.p. 321-23°), were obtained in pure form along with the product C, which analysed for a tetrazole and a lactam system. Similar reaction with ketone (**5**) obtained from **2** through alcohol (**4**), led to products A and B only. The oxime of ketone (**5**) on Beckmann rearrangement gave product C. Evidently all the three products (A, B and C) have in common the tetrazole system as in **2**. The bistetrazoles (A and B) should have structures (**6**) and (**7**), and the product C should have structure (**8**) or (**9**). In the PMR spectra of A, B and C the 18-methyl singlet appeared at about δ 1.48. The multiplets (6H) at



1 R = OCOMe, H

2 R = OCOMe, H

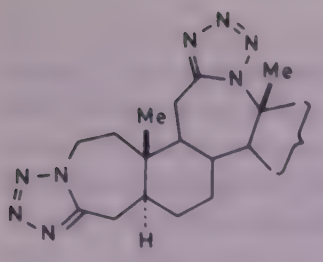
3 R = O

4 R = OH, H

5 R = O

δ 2.93-3.90 (product A) and 3.15-3.92 (product B) could be assigned to 4a-CH_2/2-CH_2, 11-CH_2 and 26-CH_2. The signal at δ 4.05-4.95 (3H, *m*) in product A and that at 4.06-4.65 (3H,*m*) in product B could be assigned to 2-CH_2/4a-CH_2 and 16α-H. In product C a six-proton multiplet at δ 3.10-3.88 could be due to 2-CH_2/4a-CH_2, 11-CH_2, and 26-CH_2.

To further rule out the lactam system in product (C) being part of ring-C, the known lactam (**10**)[12] having 3-ketone function was prepared and treated with hydrazoic acid-boron trifluoride. The reaction yielded products D (m.p. 301-3°) and E (m.p. 315-18°) both having tetrazole systems, evidently generated through Schimdt reaction with 3-ketone moiety. In product D the multiplets at δ 2.85-3.15 (2H), 3.20-3.65 (2H), and 4.05-4.95 (3H) could be due to 4a-CH_2/2-CH_2, 26-CH_2, and 16α-C*H* and 2-CH_2/4a-CH_2, respectively. In product



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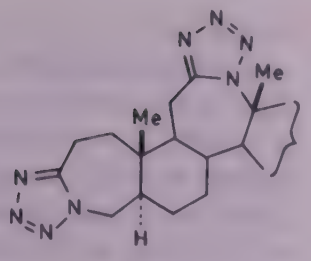

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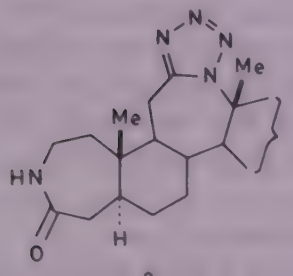

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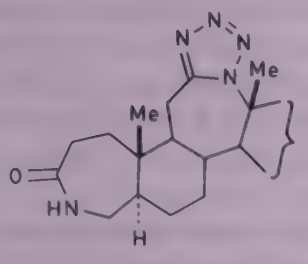

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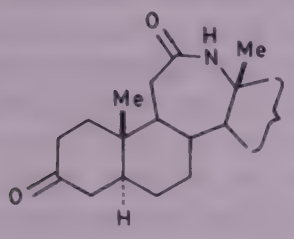

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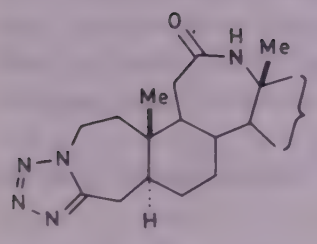

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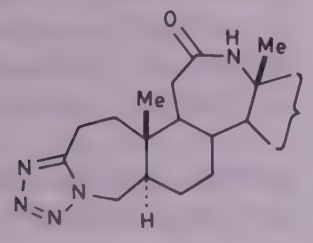

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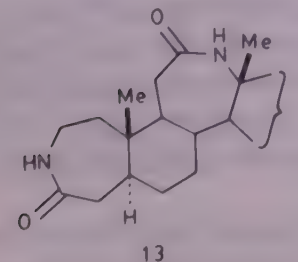
E, the multiplets appeared at δ 3.20-3.72 (4H, 2-CH_2/ 4a-CH_2, 26-CH_2) and 4.20-4.70 (3H, 16α-CH, 2-CH_2/ 4a-CH_2). On the PMR evidences the products D and E may have structures (**11**) and (**12**).

Finally, a mention may be made of a product F obtained on Beckmann rearrangement of dioxime of **3**. Since the same compound was got on Beckmann rearrangement of oxime of **10**, the product F may have structure (**13**) or (**14**).

The proof of position of nitrogen in ring-A in products A to F will come through X-ray diffraction analysis which is to be carried out on these compounds.



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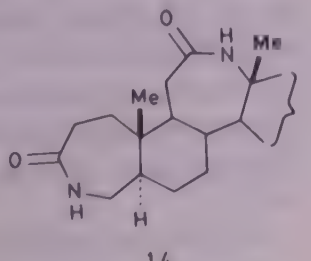

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Experimental Procedure

IR spectra were recorded in KBr and PMR spectra (90 MHz) in $CDCl_3$ with TMS as an internal standard. TLC was carried out on silica gel G (Merk); plates were developed by exposure to iodine vapour. Anhydrous sodium sulphate was employed as a drying agent.

Schmidt reaction with (25*R*)-5α-spirostan-3,12-dione (**3**)

Freshly distilled boron trifluoride-ether complex (1 ml) was added to a freshly prepared solution of hydrazoic acid (6-8%) in chloroform (60 ml) kept at 0°C. A solution of **3** (2 g) in dry chloroform (40 ml) was added in small portions during 4 hr to the above mixture maintained at 0°C. The mixture was left at room temperature (25-30°C) for 20 hr, filtered, the filtrate washed with water, dried and solvent removed to give a residue (1.9 g). TLC (Chloroform-methanol, 9 : 1) of the residue revealed seven spots, of which three were prominent. The mixture was chromatographed on a column of alumina (125 g) in dry chloroform. Elution with the same solvent yielded a residue which crystallised from methanol to give product A (**6** or **7**) (0.25 g, 10.5%), m.p. 330-32°; IR: 1515, 1485, 1425 and 1365 cm^{-1}; PMR: δ 0.80 (3H, *d*), 1.17 (3H, *s*), 1.48 (3H, *s*), 2.93-3.90 (6H, *m*) and 4.05-4.95 (3H, *m*); MS: *m/z* 508 (M^+) (Found: C, 63.8; H, 8.1; N, 21.8. $C_{27}H_{40}N_8O_2$ requires C, 63.8: H, 7.9: N, 22.0%).

Further elution with chloroform-methanol (99.8 : 0.2) gave a residue which crystallised from acetone to afford the product B (**6** or **7**) (0.14 g, 6%), m.p. 321-23°; IR: 1535; 1495, 1430 and 1365 cm^{-1}; PMR: δ 0.82 (3H, *d*), 1.18 (3H, *s*), 1.49 (3H, *s*), 3.15-3.92 (6H, *m*) and 4.06-4.65 (3H, *m*); MS: *m/z* 508 (M^+) (Found: C, 64.1; H, 8.1; N, 22.4. $C_{27}H_{40}N_8O_2$ requires C, 63.8; H, 7.9; N, 22.0%).

Further elution with chloroform-methanol (9 : 1) gave a solid which crystallised from acetone to afford the product C (**8** or **9**) (0.06 g, 2.7%), m.p. 318-20°; IR: 3250, 1650, 1520, 1460 and 1375 cm^{-1}; PMR: δ 0.80 (3H, *d*), 1.03 (3H, *s*), 1.47 (3H, *s*), 3.10-3.88 (6H, *m*), 4.50 (1H, *m*) and 6.18 (1H, *m*, exchangeable with D_2O); MS: *m/z* 483 (M^+) (Found: C, 67.3; H, 8.5; N, 14.1. $C_{27}H_{41}N_5O_3$ requires C, 67.1; H, 8.5; N, 14.5%).

(25*R*)-12*a*-*Aza*-*C*-*homo*-5α-*spirostano*[12*a*,12-*d*]-*tetrazol*-3β-*ol* (**4**)

A solution of (25*R*)-12a-aza-C-homo-5α-spirostano[12a, 12-*d*]tetrazol-3β-yl acetate (**2**)[10] (2 g) in methanol (150 ml) containing potassium hydroxide (0.4 g) was refluxed for 30 min. The reaction mixture was poured into ice-cold water (750 ml), the precipitated solid extracted with chloroform (5 × 50 ml), the combined chloroform extract washed, dried and the solvent removed to leave a residue which was

crystallised from methanol to yield **4** (1.8 g, 97.8%), m.p. 298-300°; IR: 3265, 1515, 1450 and 1385 cm^{-1}; PMR: δ 0.82 (3H, *d*), 0.97 (3H, *s*), 1.47 (3H, *s*), 1.60 (1H, exchangeable with D_2O), 3.20-3.86 (5H, *m*) and 4.53 (1H, *m*) (Found: C, 68.8; H, 8.9; N, 11.9. $C_{27}H_{42}N_4O_3$ requires C, 68.9; H, 9.0; N, 11.9%).

(25R)-12a-Aza-C-homo-5α-spirostano[12*a*, 12-*d*]-*tetrazol-3-one* (**5**)

Jones' reagent (6 ml) was added dropwise to a stirred solution of **4** (2 g) in acetone (170 ml) (distilled from permanganate) at room temperature (25-30°C). After 2-5 min the reaction mixture was diluted with water (250 ml) and extracted with chloroform (5 × 40 ml). The combined chloroform extract was washed with water, dried and solvent removed under reduced pressure to yield a residue which crystallised from methanol to give **5** (1.4 g, 70%), m.p. 255-58°; IR: 1720, 1510, 1455 and 1395 cm^{-1}; PMR: δ 0.82 (3H, *d*), 1.18 (3H, *s*), 1.50 (3H, *s*), 3.23-3.93 (4H, *m*) and 4.55 (1H, *m*) (Found: C, 69.3; H, 9.1; N, 12.2. $C_{27}H_{40}N_4O_3$ requires C, 69.2; H, 8.6; N, 12.0%).

Schmidt reaction with **5**

Freshly distilled boron trifluoride-ether complex (1.3 ml) was added to a freshly prepared solution of hydrazoic acid in chloroform (40 ml) kept at 0°C. A solution of **5** (1.5 g) in dry chloroform (45 ml) was added in small portions during 5 hr to the above mixture maintained at 0°C. After addition was complete, the reaction mixture was stirred for 1 hr and left for 20 hr at room temperature (25-30°C). The reaction mixture was filtered and washed successively with aq sodium bicarbonate (5%, 5 × 20 ml) and water. The chloroform layer was dried and solvent removed to leave a residue (1.7 g). TLC of the residue revealed five spots (Chloroform-methanol, 9.5 : 0.5).

The residue was chromatographed on a column of alumina (100 g) in chloroform. Elution with chloroform-methanol gave mixtures. The residue obtained from the column was refluxed with acetone and filtered. The solvent was removed under reduced pressure to give a residue (0.5 g) which showed to spots on TLC.

This mixture was chromatographed on a column of alumina (30 g) in chloroform. Elution with chloroform-methanol (99.5 : 0.5) yielded a residue which crystallised from methanol to afford product A (**6** or **7**) (0.01 g, 0.5%), m.p. and m.m.p. 330-33°.

Further elution with chloroform-methanol (99.25 : 0.75) gave a residue (0.08 g) which crystallised from methanol to furnish product B (**6** or **7**) (0.05 g, 2.3%), m.p. and m.m.p. 323-26°.

Oxime of **5**

A solution of sodium acetate trihydrate (1.25 g) and hydroxylamine hydrochloride (0.5 g) in water (7 ml) was added to a refluxing solution of **5** (0.5 g) in methanol (16 ml). After 4 hr the refluxing solution was allowed to cool, the separated crystals were filtered, washed with aq methanol (30%) and allowed to dry. The product so obtained was crystallised from methanol to give the oxime (0.37 g, 74%), m.p. 294-95°; IR: 3290, 1630, 1515, 1480, 1430 and 1380 cm^{-1}; PMR: δ 0.82 (3H, *d*), 1.02 (3H, *s*) 1.48 (3H, *s*), 3.20-3.90 (4H, *m*) and 4.50 (1H, *m*) (Found: C, 66.7; H, 8.6; N, 14.5. $C_{27}H_{41}N_5O_3$ requires C, 67.1; H, 8.5; N, 14.5%).

Beckmann rearrangement of oxime of **5**

A solution of thionyl chloride (0.1 ml) in dioxan (0.5 ml) was added dropwise to a stirred solution of the oxime of **5** (0.2 g) in benzene (10 ml) at 10°C. The reaction mixture was allowed to stand with stirring at 20 C for 45 min, water (10 ml) added followed by dil ammonia solution (10 ml). The benzene layer was separated and the aqueous layer extracted with chloroform (5 × 20 ml). The combined organic layer was washed with water, dried and the solvent removed under reduced pressure to leave a residue which was crystallised from methanol to give the product C (**8** or **9**) (0.15 g, 75 %), m.p. and m.m.p. 320-22 , identical with the product C obtained by the Schmidt reaction of **3**.

Schmidt reaction with (25R)-12a-Aza-C-homo-5α-spirostan-3,12-dione[12] (**10**)

Freshly distilled boron trifluoride-ether complex (1 ml) was added to a freshly prepared solution of hydrazoic acid in chloroform (60 ml) kept at 0°C. To this was added a solution of **10** (2 g) in dry chloroform (40 ml) in small portions during 4 hr at 0°C. The mixture was left at room temperature (25-30°C) for 20 hr, filtered, the filtrate washed with water, dried and solvent removed under reduced pressure to give a residue (2 g). TLC of the residue revealed six spots (chloroform-methanol, 9.5 : 0.5), of which two were prominent. The mixture was chromatographed on alumina column in benzene.

Elution with chloroform-methanol (99.5 : 0.5) yielded a residue which crystallised from methanol to afford the product D (**11** or **12**) (0.25 g, 11.4%), m.p. 301-3°; IR: 3250, 1650, 1525, 1450 and 1380 cm^{-1}; PMR: δ 0.80 (3H, *d*), 1.00 (3H, *s*), 1.38 (3H, *s*), 2.85-3.15 (2H, *m*), 3.20-3.65 (2H, *m*), 4.05-4.95 (3H, *m*) and 6.0 (1H, *m*, exchangeable with D_2O) (Found: C, 67.2; H, 8.8; N, 14.3. $C_{27}H_{41}N_5O_3$ requires C, 67.1; H, 8.5; N, 14.5%).

Elution was continued with the same solvent and the solid residue obtained was crystallised from methanol

to give the product E (**11** or **12**) (0.30 g, 13.7%), m.p. 315-18°; IR: 3250, 1650, 1530, 1450 and 1380 cm^{-1}; PMR: δ 0.80 (3H, *d*), 1.00 (3H, *s*), 1.38 (3H, *s*), 3.20-3.72 (4H, *m*), 4.20-4.70 (3H, *m*) and 6.0 (1H, *m*, exchangeable with D_2O) (Found: C, 67.6; H, 8.8; N, 14.1. $C_{27}H_{41}N_5O_3$ requires C, 67.1; H, 8.5; N, 14.5%).

Dioxime of **3**

A solution of sodium acetate trihydrate (5 g) and hydroxylamine hydrochloride (2 g) in water (30 ml) was added to a refluxing solution of **3** (2 g) in methanol (120 ml). After 4 hr the refluxing solution was allowed to cool, the solid obtained filtered, washed with aq methanol (30%) and allowed to dry. The product so obtained was crystallised to afford the desired dioxime of **3** (1.7 g, 80.9%), m.p. 299-301°; IR: 3245 and 1640 cm^{-1}; PMR: δ 0.82 (3H, *d*) 1.00 (6H, *s*), 3.48 (2H, *m*), 4.50 (1H, *m*) and 8.78 (*m*, exchangeable with D_2O) (Found: C, 70.8; H, 9.3; N, 6.0. $C_{27}H_{42}N_2O_4$ requires C, 70.7; H, 9.2; N, 6.1%).

Beckmann rearrangement of the dioxime of **3**

A solution of thionyl chloride (0.5 ml) in dioxan (2.5 ml) was added dropwise with stirring to a solution of the dioxime of **3** (1 g) in benzene (20 ml) at 15°C. The mixture was allowed to stand with stirring at 20°C for 35 min, water (25 ml) added followed by dil ammonia solution (50 ml). The benzene layer was separated and the aqueous layer extracted with chloroform (5 × 20). The combined organic layer was washed with water, dried and solvent removed under reduced pressure to leave a residue (1.2 g).

The residue on TLC showed two spots (chloroform-methanol, 9.5 : 0.5) of which one was prominent. The mixture was chromatographed on a column of alumina in chloroform. Elution with chloroform-methanol (98:2) gave a residue (0.5 g) which on crystallisation from chloroform afforded the product F(**13** or **14**) (0.45 g, 25%), m.p. 312-14°; IR: 3215 and 1640 cm^{-1}; PMR: δ 0.82 (3H, *d*), 0.87 (3H, *s*), 1.36 (3H, *s*) 3.10-3.60 (4H, *m*), 4.50 (1H, *m*), 6.00 (1H, *m*, exchangeable with D_2O) and 6.20 (1H, *m*, exchangeable with D_2O) (Found: C, 70.4; H, 9.3; N, 6.2. $C_{27}H_{42}N_2O_4$ requires C, 70.7; H, 9.2; N, 6.1%).

3-*Oxime of* **10**

A solution of sodium acetate trihydrate (1.25 g) and hydroxylamine hydrochloride (0.5 g) in water (7 ml) was added to a refluxing solution of **10** (0.5 g) in methanol (15 ml) and refluxing was continued for 4 hr. The reaction mixture was cooled and separated crystals were filtered, washed with aq methanol (30%), allowed to dry and crystallised from methanol to give the 3-Oxime of **10** (0.45 g, 87.0%), m.p. 201-3°; IR. 3300, 3125 and 1640 cm^{-1}; PMR: δ 0.82 (3H, *d*), 1.00 (3H, *s*), 1.36 (3H, *s*), 3.30-3.65 (2H, *m*), 4.50 (1H, *m*) and 6.00 (1H, *m*, exchangeable with D_2O) (Found: C, 71.5; H, 9.3; N, 5.9. $C_{27}H_{42}N_2O_4$ requires C, 70.7; H, 9.2; N, 6.1%).

Beckmann rearrangement of 3-*oxime of* **10**

A solution of thionyl chloride (0.2 ml) in dioxan (1 ml) was added dropwise with stirring to a solution of the 3-oxime of **10** (0.4 g) in benzene (7 ml) at 15°C. The reaction mixture was allowed to stand with stirring at 20° for 35 min, water (10 ml) added followed by dil ammonia solution (20 ml). The benzene layer was separated and the aqueous layer extracted with chloroform (5 × 20 ml). The combined organic layer was washed with water, dried and solvent removed — under reduced pressure to leave a residue which was crystallised from methanol to yield the product F (**13** or **14**) (0.30 g, 75%), m.p. 310-14°; IR: 3215 and 1640 cm^{-1}; PMR: δ 0.82 (3H, *d*), 0.87 (3H, *s*), 1.36 (3H, *s*), 3.10-3.60 (4H, *m*), 4.50 (1H, *m*), 6.00 (1H, *m*, exchangeable with D_2O) and 6.20 (1H, *m*, exchangeable with D_2O) (Found: C, 70.2; H, 9.2; N, 6.1. $C_{27}H_{42}N_2O_4$ requires C, 70.7; H, 9.2; N, 6.1%).

Acknowledgement

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Condensation of Phenols & Cinnamic Acids in Presence of Polyphosphoric Acid: A Novel Biogenetic-type Oxidative Self-cyclisation of *p*-Methoxycinnamic Acid to 7-Methoxycoumarin

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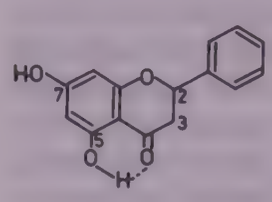
The course of PPA condensation/cyclisation of different phenols and cinnamic acids has been found to depend upon the nature of the substrate, stoichiometry, composition of PPA, and reaction condition. Condensation of phloroglucinol (50-70°, 1 hr) with cinnamic acid in the presence of PPA leads to pinocembrin(I) (50%) and 5-hydroxy-4,8-diphenyl-3,4,6,7-tetrahydro-2*H*,6*H*-benzo[1,2-*b*: 5,4-*b*']dipyran-2,6-dione (II) (14%). This condensation reaction when carried out with resorcinol for 2 hr furnishes 7-hydroxyflavanone (III) (60%). Condensation of resorcinol monomethyl ether affords 2'-hydroxy-4'-methoxychalcone (IV) (12%) and 4'-hydroxy-2'-methoxychalcone (V) (40%), but no flavanone derivative. Reaction of *p*-methoxycinnamic acid (in xylene), in the presence of PPA and resorcinol, however, yields 7-hydroxy-4-(4'-methoxyphenyl)-3,4-dihydrocoumarin (VI) (56%); with resorcinol monomethyl ether the corresponding 7-methoxy derivative (VII) (44%) is obtained. Further, *p*-methoxycinnamic acid undergoes self-condensation in the presence of 0.5 mol equiv of phloroglucinol or resorcinol to give *p*-methoxycinnamic anhydride (VIII) (only 4%) or bis(4-methoxybenzal) acetone (IX) (50%). Interestingly, in the presence of resorcinol monomethyl ether (0.5 mol equiv, 4 hr) *p*-methoxycinnamic acid undergoes biogenetic-type oxidative self-cyclisation to form 7-methoxycoumarin (X) (80%). A plausible mechanism for the formation of X has been suggested.

Recently we reported the synthesis of pinocembrin[1] (I) in 50% yield involving the condensation of phloroglucinol with cinnamic acid in the presence of polyphosphoric acid (PPA). A minor product (14%) purified through chromatography and crystallisation, was also isolated along with I, and it was assigned the structure 5-hydroxy-4,8-diphenyl-3,4,6,7-tetrahydro-2*H*,6*H*-benzo[1,2-*b*: 5,4-*b*']dipyran-2,6-dione (II) primarily on the basis of its PMR and mass spectral data. Formation of II, m.p. 180° (M^+ 386) prompted us to undertake the PPA cyclisation of various phenols with cinnamic acid and *p*-methoxycinnamic acid, the results of which are presented in this paper.

Literature survey[2,3] and identification of products mainly on the basis of their PMR and mass spectral analysis showed that the course of such a reaction with PPA is dependent on several factors, viz. nature of the substrate, stoichiometry, composition of PPA, temperature, solvent etc.

7-Hydroxyflavanone (III) has previously been synthesised[2,4] by the condensation of resorcinol with cinnamic acid in the presence of PPA in 12.7% and 20% yields, respectively when the condensation was carried out for 25 min at 85-95° and 100°. A three to five-fold increase in the yield (60%) has now been achieved by lowering the temperature to 50-70° and increasing the reaction period to 2 hr.

Similar condensation of monomethyl ether of resorcinol led to a chromatographically separable mixture of isomeric chalcones identified as 2'-hydroxy-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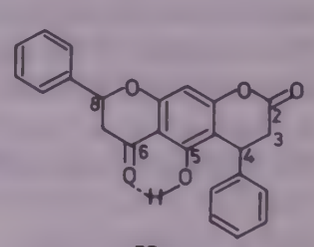
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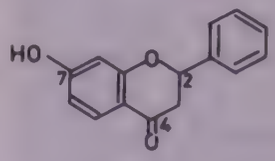
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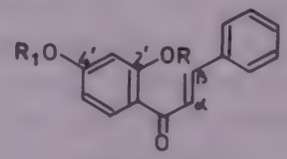
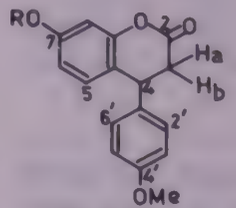

IV R=H, R_1=Me
V R=Me, R_1=H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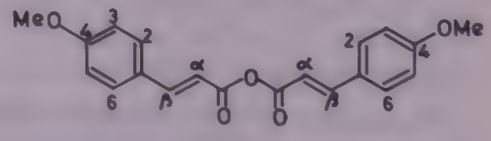
VII R = Me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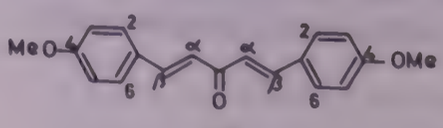
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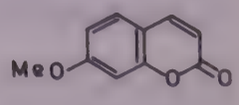

X

4'-methoxychalcone (IV) (12%) and 4'-hydroxy-2'-methoxychalcone (V) and no flavanone derivative could be isolated from the mixture. Fortuitously this observation has been found to be similar to some extent to that of Reichel and Proksch[5] who obtained IV only in 11% yield as the sole product.

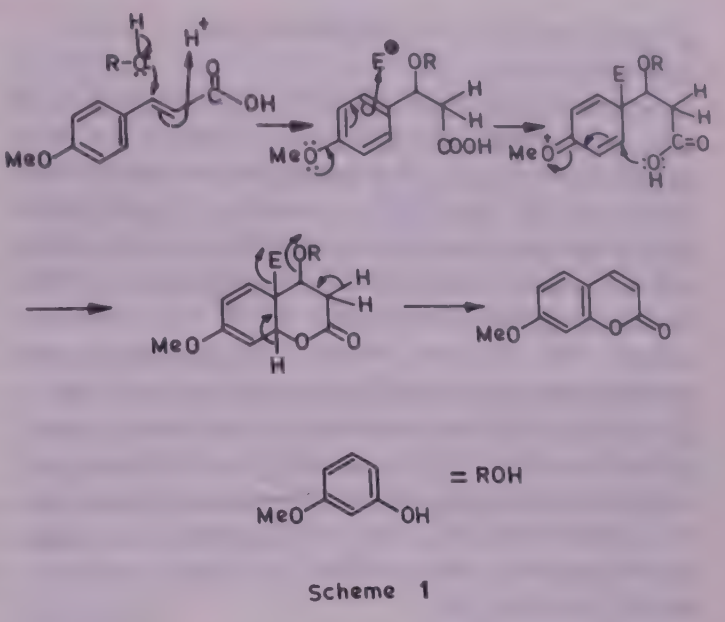
However, when the same reaction was carried out with *p*-methoxycinnamic acid, resorcinol and PPA in xylene at 70° for 1 hr neither the corresponding chalcone nor the flavanone could be isolated from the reaction mixture. Instead a coumarin derivative identified as 7-hydroxy-4-(4'-methoxyphenyl)-3,4-dihydrocoumarin (VI), was obtained in 56% yield. VI on methylation furnished the corresponding methyl ether (VII) which could also be obtained in 44% yield from the reaction of resorcinol monomethyl ether with *p*-methoxycinnamic acid in the presence of PPA. Formation of such 4-phenylcoumarin derivative has recently been reported by Matsui[2] from resorcinol and cinnamic acid in the presence of PPA.

Unlike cinnamic acid, *p*-methoxycinnamic acid did not react with phloroglucinol under our normal experimental condition or even under comparatively drastic condition. Instead it underwent self-dimerization to afford *p*-methoxycinnamic anhydride (VIII) in 4% yield through the elimination of the elements of water while phloroglucinol was isolated almost quantitatively from the reaction mixture. Similar anhydride formation in the presence of PPA from diethyl phthalate and diethyl maleate was reported earlier[6].

p-Methoxycinnamic acid was reported[7] to be converted into its *cis*-isomer when heated with PPA at 100°. In our hand at 60-70° (4 hr) *p*-methoxycinnamic acid gave bis(4-methoxybenzal)acetone (IX) in 20% yield. The yield of IX was considerably increased (50%) on heating *p*-methoxycinnamic acid with resorcinol in the ratio 2:1 at 60-70° for 1 hr and resorcinol was quantitatively recovered.

However, the most striking observation was that *p*-methoxycinnamic acid upon heating with PPA in the presence of resorcinol monomethyl ether formed 7-methoxycoumarin (X) in 80% yield, but unreacted resorcinol monomethyl ether was recovered from the reaction mixture. Interestingly, the formation of 7-methoxycoumarin did not take place in the absence of resorcinol monomethyl ether.

In all the above cases where the products are just derived from *p*-methoxycinnamic acid, quite intriguing are the effects of phenols like phloroglucinol, resorcinol and resorcinol monomethyl ether. The exact role of these phenols in this reaction appears difficult to decipher. However, we believe that during the conversion of *p*-methoxycinnamic acid into 7-methoxycoumarin in the presence of resorcinol monomethyl ether and PPA, the reaction proceeds through the addition of resorcinol monomethyl ether across the cinnamic acid double bond- as has been observed[8] in the acetoxylation of olefins with acetic acid in the presence of PPA-and the capture of an electrophile at the position *para* to the methoxy of the aromatic ring to activate the *meta* position for an internal nucleophilic attack by COOH group. This is followed by the elimination of the electrophile and a proton to effect the aromatisation as well as the elimination of resorcinol monomethyl ether to generate coumarin double bond to form X. This rationalisaton (Scheme 1) finds analogy in the biogenetic-type conversion of *p*-methoxycinnamic acid to 7-methoxycoumarin, although the sequence of the chemical events are unpredictable. However, the presence of a methoxy group in cinnamic acid at *para* position imputes a vital role in the consequence of the reaction and to our knowledge such lactone formation during PPA cyclisation has not been reported in the literature.



Scheme 1

Experimental Procedure

Melting points were taken in open capillaries in an electrical metal bath and are uncorrected. IR spectra were recorded in KBr (ν_{max} in cm^{-1}) on a Perkin-Elmer 782 spectrophotometer and PMR spectra in $CDCl_3$ on Varian CFT-20 (80 MHz), Varian XL-200 (200 MHz) and Bruker-300 (300 MHz) instruments using TMS internal reference: chemical shift in δ-scale. Mass spectra were recorded on a JEOL JMS-D-300 spectrometer fitted with JEOL JMA-200 data processing system. Column chromatography was carried over silica gel (60-120 mesh). The compounds were crystallised from chloroform-petrol mixture, unless otherwise stated. Petrol refers to light petroleum, b.p. 60-80°.

General method for polyphosphoric acid mediated reactions

To the freshly prepared PPA [from P_2O_5 (12.5 g) and orthophosphoric acid (*d* 1.75 g/ml, 7 g ≈ 4 ml), stirred vigorously to get a homogeneous mixture and heated at 100° for 2 hr] a mixture of appropriate phenol and cinnamic acid or its derivative was added with stirring at room temperature (in the case of VI the starting materials were added to the PPA in anhydrous xylene). The reaction mixture was heated at the required temperature and time period listed in Table 1. The reaction mixture was cooled to room temperature, crushed ice added, left overnight, extracted with ether or methylene chloride, the organic extract washed with brine, dried (Na_2SO_4) and concentrated. The crude product/products were purified by column chromatography on silica gel.

Pinocembrin (I), m.p. 194°; IR (KBr): 3100, 1640, 1610, 1585, 1500, 1310, 1175, 1090, 830, 720; PMR ($CDCl_3$, 80 MHz): 12.04 (1H, *s*, disappeared with D_2O; 5-OH), 7.44 (5H, *bs*, B-ring protons), 6.02 (2H, *s*, H-6, H-8), 5.44 (1H, *dd*, $J = 4$ and 11 Hz, H-2ax), 3.15 (1H, *dd*, $J = 11$ and 18 Hz, H-3ax), 2.74 (1H, *dd*, $J = 4$ and 18 Hz, H-3eq); MS: *m/z* 256 (M^+, 71%), 255 (62), 179 (98), 152 (100).

5-Hydroxy-4,8-diphenyl-3,4,6,7-tetrahydro-2H, 6H-benzo [1,2-*b*: 5,4-*b*'] dipyran-2,6-dione(II), m.p. 180°; IR (KBr): 3520-3380, 1760, 1640, 1590, 1530, 1490, 1475, 1440, 1368, 1345, 1288, 1240, 1210, 1150, 1095, 760, 695; PMR ($CDCl_3$, 300 MHz): 12.2 (1H, *s*, disappeared with D_2O, 5-OH), 7.3 (5H, *m*, $-C_6H_5$), 7.2 (5H, *m*, $-C_6H_5$), 6.2 (1H, *s*, H-10), 5.5 (1H, *m*, H-8), 4.7 (1H, *m*, H-4), 3.2-2.8 (4H, *m*, H_2-3 and H_2-7); MS: *m/z* 386 (M^+, 91%), 385 (81.5), 358 (70.9), 344 (20.0), 343(47.6), 309 (76.3), 282(63.8), 281 (40.7), 254(70.5), 239 (80.0), 104(53.5), 77(57.2), 28(100).

7-Hydroxyflavanone (III), m.p. 194°; IR (KBr): 3100-2600, 1650, 1610, 1570, 1490, 1330, 1310, 1298, 1260, 1165, 1110, 1000, 852, 800, 765, 750, 690, 670; PMR ($CDCl_3$, 80 MHz): 7.85 (1H, *d*, $J = 8.3$ Hz, H-5), 7.4 (5H, *bs*, $-C_6H_5$), 6.53 (1H, *d*, $J = 8.3$ Hz, H-6), 6.48 (1H, *bs*, H-8), 5.46 (1H, *dd*, $J = 4.3$ and 11.3 Hz, H-2ax), 3.05 (1H, *dd*, $J = 11.3$ and 16 Hz, H-3ax), 2.75 (1H, *dd*, $J = 4.3$ and 16 Hz, H-3eq); MS: *m/z* 240 (M^+, 100%), 239 (72.4), 163 (74.3), 136 (91.3), 108 (39.65), 104 (65.55), 77 (25.9).

2'-Hydroxy-4'-methoxychalcone (IV), m.p. 108°; IR (KBr): 1630, 1570, 1490, 1440, 1358, 1270, 1218, 1130, 1010, 952, 848, 800, 760, 730, 685, 670; PMR ($CDCl_3$, 80 MHz): 13.42 (1H, *s*, exchangeable with D_2O, 2'-OH), 7.9 (1H, *d*, $J = 15.5$ Hz, H-β), 7.89-7.38 (6H, *m*, H-6' and $-C_6H_5$), 7.55 (1H, *d*, $J = 15.5$ Hz, H-α), 6.49(1H, *dd*, $J = 2.4$ and 9.5 Hz, H-5'), 6.47 (1H, *d*, $J = 2.4$ Hz, H-3'), 3.86 (3H, *s*, 4'-OCH_3); MS: *m/z* 254 (M^+, 95.7%), 253 (100), 177 (94.8), 151 (89.3), 150 (80.6), 131 (53.5), 104 (43.6), 103 (80.8), 77 (84.9).

4'-Hydroxy-2'-methoxychalcone (V), m.p. 142°; IR (KBr): 3100 (br), 1630, 1605, 1570, 1540, 1462, 1372, 1320, 1250, 1200, 1170, 1120, 1030, 968, 828, 758, 730, 690; PMR ($CDCl_3$, 80 MHz): 7.71 (1H, *d*, $J = 15.9$ Hz, H-β), 7.66 (1H, *d*, $J = 8.8$ Hz, H-6'), 7.44 (1H, *d*, $J = 15.9$ Hz, H-α), 7.5-7.3 (5H, *m*, $-C_6H_5$), 6.51 (1H, *dd*, $J = 2$ and 8.8 Hz, H-5'), 6.49 (1H, *bs*, H-3'), 3.82 (3H, *s*, 2'-OCH_3).

7-Hydroxy-4-(4'-methoxyphenyl)3,4-dihydrocoumarin (VI), m.p. 150°; IR (KBr): 3500-3380, 1760, 1625, 1610, 1590, 1510, 1460, 1432, 1320, 1270, 1250, 1220, 1190, 1175, 1160, 1130, 1108, 1035, 978, 968, 885, 840, 830, 820; PMR ($CDCl_3$, 200 MHz): 7.08 (2H, *d*, $J = 8$ Hz, H-2' and H-6'), 6.9 (2H, *d*, $J = 8$ Hz, H-3' and H-5'), 6.48 (1H, *d*, $J = 9$ Hz, H-5), 6.6 (1H, *d*, $J = 3$ Hz, H-8), 6.58 (1H, *dd*, $J = 3$ and 9 Hz, H-6), 5.0 (1H, *s*, exchangeable with D_2O, 7-OH), 4.25 (1H, *t*, unsymmetrical, $J = 6$ and 7 Hz, H-4), 3.82 (3H, *s*, 4'-OCH_3), 3.06 (1H, *dd*, $J = 6$ and 16 Hz, H_a-3), 2.96 (1H, *dd*, $J = 7$ and 16 Hz, H_b-3); MS: *m/z* 270 (M^+, 100%), 242 (15.1), 227 (44.5).

Table 1—Condensation Reactions of Phenols with Cinnamic Acids in Presence of PPA

Phenol	Acid	Product(s)	Yield (%)	Reaction temp. (°C)	Reaction time (hr)
Phloroglucinol	Cinnamic acid	I*	50	50-70	1
		II*	14		
Resorcinol	-Do-	III*	60	50-70	2
Resorcinol monomethyl ether	-Do-	IV*	12	70	2
		V*	40		
Resorcinol	*p*-Methoxycinnamic acid	VI*	56	70(in xylene)	1
		IX†	50	60-70	1
Resorcinol monomethyl ether	*p*-Methoxycinnamic acid	VII*	44	70	1
		X†	80	70	4
Phloroglucinol	*p*-Methoxycinnamic acid	VIII†	4	70	1

*Phenol: acid :: 1:1. †Phenol: acid :: 1:2.

7-Methoxy-4-(4′-methoxyphenyl)3,4-dihydrocoumarin (VII), m.p. 134°; IR(KBr): 1750, 1620, 1600, 1570, 1500, 1450, 1425, 1320, 1310, 1290, 1280, 1260, 1240, 1210, 1180, 1165, 1150, 1120, 1095, 1025, 965, 955, 875, 830, 820, 805, 760, 740, 700, 622; PMR ($CDCl_3$, 200 MHz): 7.12 (2H, *d*, $J = 8$ Hz, H-2′ and H-6′), 6.92 (3H, *d*, $J = 8$ Hz, H-5, H-3′ and H-5′), 6.67 (1H, *d*, $J = 3$ Hz, H-8), 6.64 (1H, *dd*, $J = 3$ and 8 Hz, H-6), 4.24 (1H, *t*, unsymmetrical, $J = 6$ and 8 Hz, H-4), 3.81 (6H, *s*, 4′ and 7-OCH_3), 3.08 (1H, *dd*, $J = 6$ and 16 Hz, H_a-3), 2.96 (1H, *dd*, $J = 8$ and 16 Hz, H_b-3).

p-Methoxycinnamic anhydried (VIII), m.p. 155°; IR (KBr): 1775, 1730, 1625, 1510, 1440, 1250, 1170, 1120, 1065, 1030, 820; PMR ($CDCl_3$, 80 MHz): 7.71 (2H, *d*, $J = 15.9$ Hz, H-β), 7.47 (4H, *d*, $J = 8.6$ Hz, H-2 and H-6), 6.95 (4H, *d*, $J = 8.6$ Hz, H-3 and H-5), 6.28 (2H, *d*, $J = 15.9$ Hz, H-α), 3.82 (6H, *s*, 4-OCH_3).

Bis(4-methoxybenzal)acetone (IX), m.p. 120°; IR(KBr): 1650, 1625, 1595, 1570, 1505, 1415, 1290, 1245, 1110, 1030, 980, 830, 820, 808, 768, 752; PMR ($CDCl_3$, 200 MHz): 7.7 (2H, *d*, $J = 16$ Hz, H-β), 7.58 (4H, *dd*, $J = 2$ and 7 Hz, H-2 and H-6), 6.96 (2H, *d*, $J = 16$ Hz, H-α), 6.92 (4H, *dd*, $J = 2$ and 7 Hz, H-3 and H-5), 3.86 (6H, *s*. 4-OCH_3); MS: *m/z* 294 (M^+, 87.59%) 161 (32.59), 133 (34.7), 28 (100).

7-Methoxycoumarin (X), m.p. 118° (acetone-petrol); IR (KBr): 1720, 1610, 1502, 1460, 1440, 1400, 1350, 1280, 1235, 1210, 1155, 1120, 1100, 1028, 980, 890, 850, 830, 760, 750, 685, 630, 620; PMR ($CDCl_3$, 80 MHz): 7.58 (1H, *d*, $J = 9.5$ Hz, H-4), 7.32 (1H, *d*, $J = 9.3$ Hz, H-5), 6.81 (1H, *dd*, $J = 2.3$ and 9.3 Hz, H-6), 6.76 (1H, *d*, $J = 2.3$ Hz, H-8), 6.2 (1H, *d*, $J = 9.5$ Hz, H-3), 3.83 (3H, *s*, 7-OCH_3).

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Heterocyclic Quinonoid Chromophoric Systems: Part VII†—Reaction of 2,3-Dichloro-1,4-naphthoquinone with Nitromethane & Vinylogously Substituted Nitromethanes, Di- & Trinitrotoluenes‡

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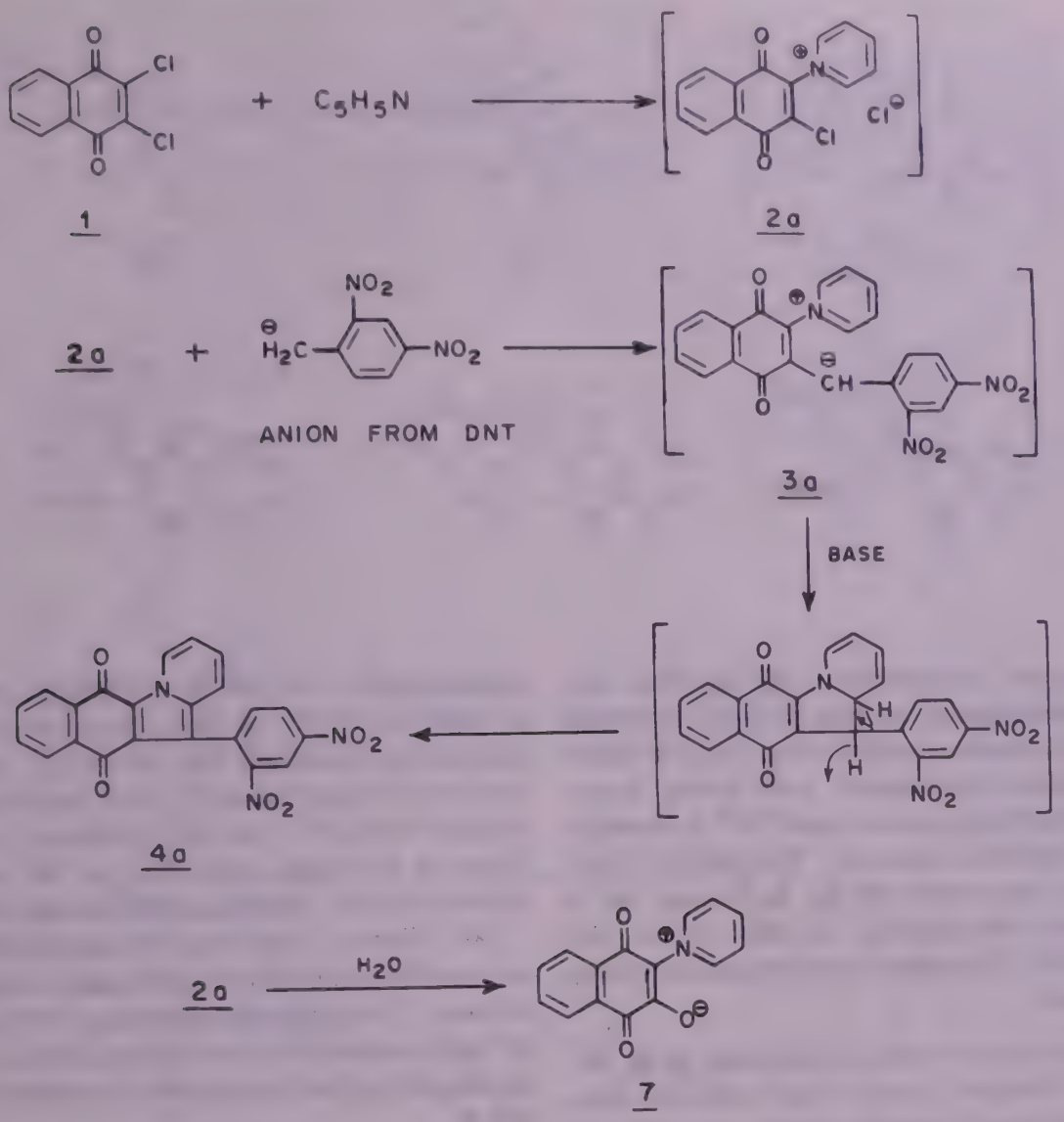
Interaction of 2,3-dichloro-1,4-naphthoquinone (**1**) with nitromethane and nitrotoluenes (DNT and TNT) containing a reactive methylene group in the presence of heterocyclic bases affords the nitro- and nitroaryl-naphthindolizinediones (**4a-j**, **5a-d**, and **6a,b**). The compounds are selectively reduced to give amino- and aminoaryl-napthindolizinediones. Their acetyl, benzoyl and bis-cyanoethyl derivatives have also been reported. Effect of solvent in the formation of naphthindolizinediones has been discussed.

The indolizine nucleus is gaining importance due to its incorporation in chromogens[1,2] and its presence in biologically active ergot-type alkaloids[3]. Major synthetic routes to indolizines fused to quinonoid moieties producing naphthindolizinediones have been reported by us[1,2]. Recently, we have reported the synthesis of 12-substituted naphthindolizinediones by the interaction of 2,3-dichloro-1,4-naphthoquinone (**1**) with methyl substituted heterocyclic bases, and other open chain and cyclic compounds containing a reactive methylene group[4,5]. Although the cyclization with various reactive methylene compounds has been reported, the reactions of **1** with nitro activated carbon acids such as nitromethane and vinylogously substituted nitromethanes like 2,4-dinitrotoluene (DNT) and 2,4,6-trinitrotoluene (TNT) have not yet been fully explored.

In the present paper further evidence for the methyl group participation in the preparation of naphthindolizinedione has been documented. Thus, the interaction of **1** with DNT is boiling dioxan in the presence of pyridine gave 12-(2′,4′-dinitrophenyl)naphth[2,3-*b*]indolizine-6,11-dione (**4a**) (30%) together with the betaine salt (**7**). The formation of **4a** from DNT can be rationalized in terms of known reactive methylene group chemistry, involving initial attack by an anion on the pyridinium salt (**2a**) (Scheme 1). The delocalized zwitterion (**3a**), thus produced, undergoes cyclization to give **4a**. The formation of a blue coloured zwitterionic species was confirmed during the reaction of **1** with homophthalimide[5]. The structure **4a** was established by spectral (IR, PMR and MS)** data and elemental analysis. The PMR spectrum of **4a** in $AsCl_3$ displayed a characteristic doublet at 9.8 due to the proton adjacent to the nitrogen of indolizine nucleus (C_4-H), a multiplet in the region 7.0-8.4 due to seven protons at C-1 to C-3 and C-7 to C-10, a doublet at 9.0 ($J=2$ Hz) due to a proton at C-3′ situated between the two nitro groups of DNT moiety, and doublets at 8.6-8.9 assignable to the two protons at C-5′ and C-6′ of DNT unit. In the IR spectrum of **4a**, in nujol, the carbonyl frequencies appeared at 1650 and 1630. Its mass spectrum showed molecular ion (base peak) at m/z 413. The fragmentation pattern clearly showed the loss of two nitro groups which confirmed their presence in the molecule (**4a**). The structure of **4a** was finally confirmed by an independent synthesis from 2,4-dinitrobenzylpyridinium bromide and the pyridinium salt **2a**. The interaction of 2,4-dinitroethylbenzene with **1** in the presence of pyridin gave an orange solid which was found to be identical with **4a**. The formation of **4a** in this case indicates that the zwitterion formed undergoes cyclization to **4a** by the loss of methane molecule. The yield of **4a** in this was only reaction 3-4%.

In efforts to improve the yield of **4a**, the reaction of **1** with DNT in pyridine was repeated in different bases and different solvents. Thus, when dimethylformamide, dimethylsulphoxide and ethanol were used as solvents, **4a** could be isolated only in trace amounts, the major product being the betaine **7**. The formation of **4a** in benzene, toluene, chlorobenzene and xylene was found to be in 8, 12, 17 and 27% yields respectively. The cyclization in boiling dioxan gave **4a** in 30% yield. Various other bases were also examined for the cyclisation reaction, but were all unsatisfactory. Thus, the use of triethylamine and sodamide failed to give the required **4a**.

†Part VI, *Indian J Chem*, **19B** (1980) 836.
‡NCL Communication No. 3925.
**Chemical shifts are in δ ppm and IR ν_{max} in cm^{-1}

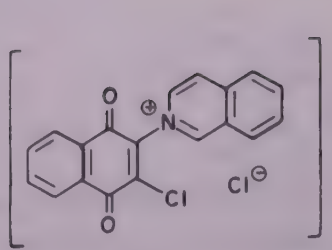


SCHEME 1

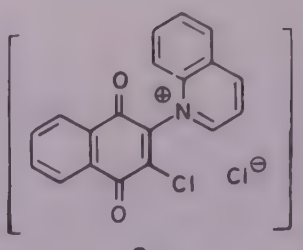
The presence of more than one electron-withdrawing group in toluene increases the acidity and accordingly increases the reactivity of the anion formed. This is best exemplified by the fact that mononitro-, monocyano- and monocarbomethoxytoluenes failed to give the required naphthindolizinediones under identical conditions. On the other hand TNT and 2-cyano-4-nitrotoluene (CNT) reacted rapidly with pyridinium salt (**2a**) to give naphthindolizinediones **4b** and **4c** in 30 and 25% yields respectively.

When the reaction of **1** was carried out in isoquinoline, the yields of the desired naphthindolizinediones were markedly changed. Thus, when the isoquinolyl salt **2b** was treated with DNT, TNT and CNT, the products **5a**, **5b** and **5c** were obtained in 20, 10 and 9% yields respectively. This is in contrast to our earlier reports in which the yields of naphthindolizinediones were better when pyridine was replaced by isoquinoline[3]. The low yields in the present case may be attributed to the increased steric interactions inhibiting resonance in the crowded carbanions of DNT, TNT and CNT. The interaction of quinolyl salt **2c** with active methylene groups normally yields naphthindolizinediones in very poor yields. Thus, DNT on interaction with **2c** gave 7-(2′,4′-dinitrophenyl)benz[5,6]indolo[1,2-*a*]quinoline-8,13-dione (**6a**) in 6% yield.

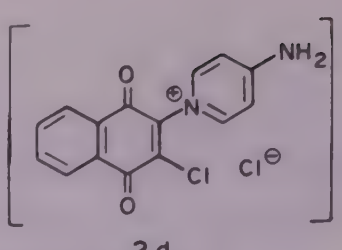
Replacement of pyridine in the above reactions by substituted pyridine did not lead to improved yields of the relevant naphthindolizinediones. When DNT, TNT or CNT were reacted with chloro or cyanopyridinium salts of **1**, the formation of the corresponding naphthindolizinediones could not be noticed. With ethyl isonicotinate and 4-acetamidopyridine, the desired compounds (**4d-4f**) could be isolated in 5 to 6% yields. However, when the reaction was conducted in highly basic 4-aminopyridine (pK_a = 9.17) very complex reaction mixture was obtained. Thus, with CNT and 4-aminopyridyl salt (**2d**), 2-amino-12-(2′-cyano-4′-nitrophenyl)naphth[2,3-*b*]indolizine-6,11-dione (**4g**) was isolated in only 2% yield. The low yields of the desired products in highly



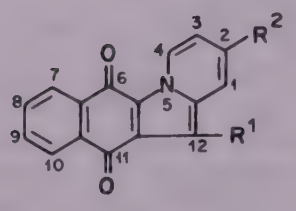
2b



2c



2d



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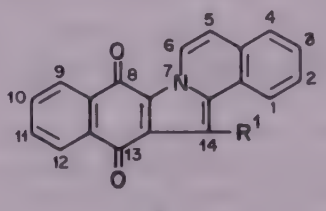

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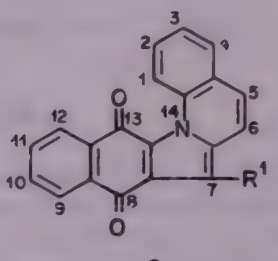


6

basic medium are in agreement with the fact that substituted nitrotoluenes are very sensitive to strong bases. Several competing reactions are likely to occur when nitrotoluenes are treated with strong bases. Formation of several products from TNT in strongly basic medium has been reported[6]. The pattern of the yields for the compounds **4b-4g**, **5a-5c** and **6a** in various solvents was identical to that of **4a**. The optimum yields in all the cases were obtained in boiling xylene or dioxan.

The yellow to violet coloured compounds **4a-4g**, **5a-c** and **6a** were obtained in crystalline form and their structures ascertained through their spectral and elemental data. A characteristic doublet due to the proton adjacent to the nitrogen of indolizine nucleus was consistently found in every spectrum of the above naphthindolizinedione derivatives.

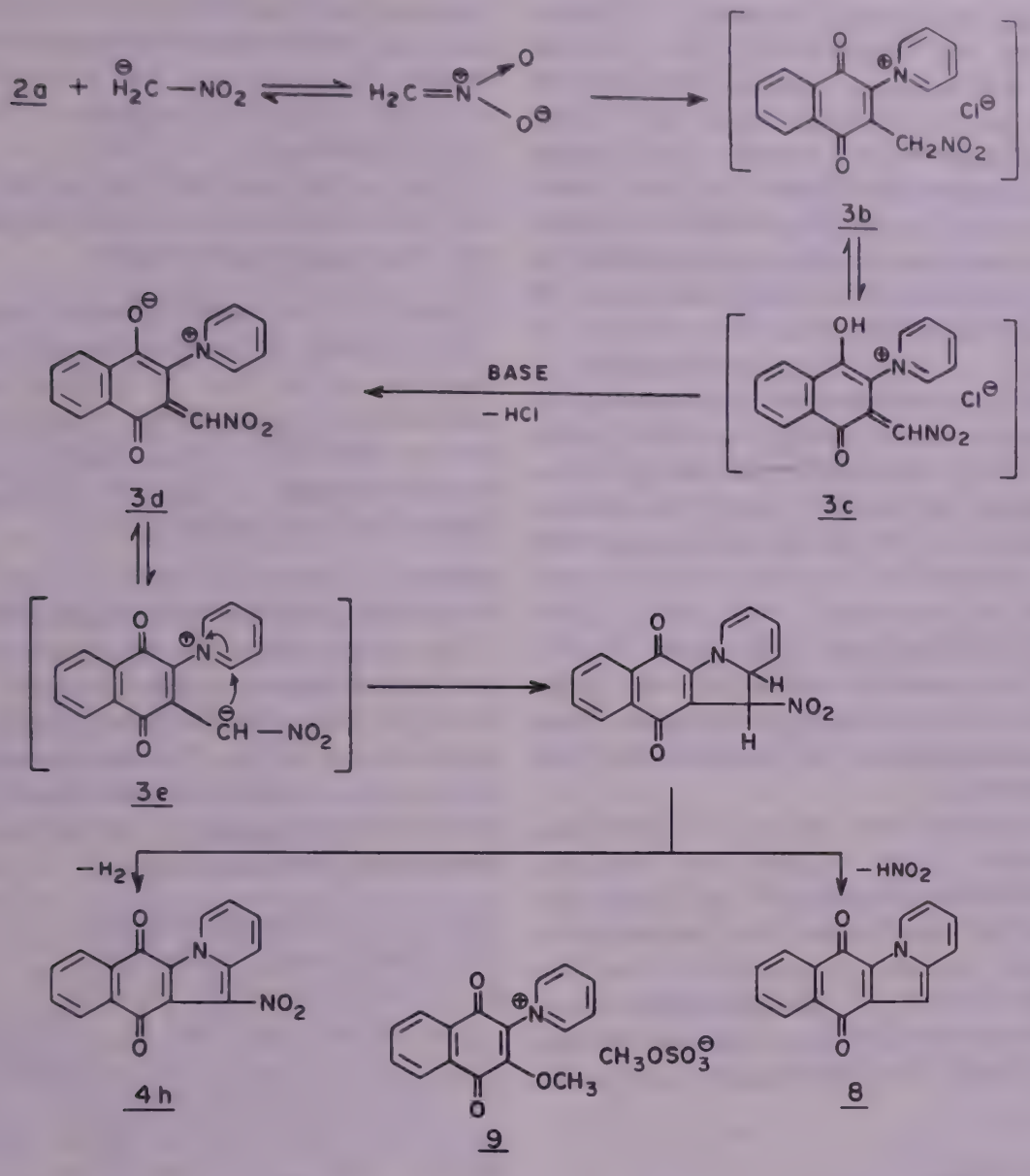
The present study on the interaction of vinylogously substituted nitromethanes was further extended to simple nitromethane. Thus, a clear solution of **1** in nitromethane on treatment with three equivalents of pyridine gave the desired 12-nitronapth[2,3-*b*]indolizine-6,11-dione (**4h**) in 35% yield. The mechanism of formation of **4h** is outlined in Scheme 2. The blue colouration observed during the reaction is characteristic of zwitterionic species. The zwitterion **3d** which is isoelectronic with **3e** ultimately undergoes ring closure with the elimination of a hydrogen molecule to give **4h**. Reynolds *et al.*[7] have reported that N-(1,4-dioxo-2-methoxy-3-naphthyl)pyridinium methosulphate (**9**) reacts with nitromethane to give **4h**. The yields of **4h** by this route was not mentioned. Repeating this reaction between **9** and nitromethane, we obtained **4h** in only 20% yield. Earlier attempt[8] to synthesise **4h** by the interaction of **1** and nitromethane in isoquinoline resulted in the parent naphth[2,3-*b*]indolizine-6,11-dione (**8**). Although a patent reports an yield of 65-79% of **4h** by nitration of this parent naphthindolizinedione (**8**), the latter could not be obtained in more than (40% yield starting from **1**. The reaction between **1** and nitromethane to give **4h** was found to be highly dependent on the nature of the solvent and the reaction period as shown in Table 1.

The failure of Pratt *et al.*[8] to isolate **4h** from **1**, and nitromethane can now be attributed to their use of high boiling 1,2,3-trichloropropane (b.p. 148°) as a solvent. At high temperature the intermediate zwitterion (**3e**) undergoes cyclization with the elimination of HNO_2 to give **8**.

The interaction of **1** with nitromethane was then carried out in other heterocyclic bases. Thus, the required naphthindolizinediones **5d**, **6b**, **48** and **4j** were obtained in 35, 16, 16 and 13% yields when the reaction was conducted in isoquinoline, quinoline, ethyl isonicotinate and 4-cyanopyridine respectively. The variation in yields of the above compounds in different solvents followed the same pattern as noticed in the

Table 1—Effect of Solvent and Reaction Period on the Formation of **4th**

Solvent	Reaction period (hr)	% yield of **4h**	% yield of **8**
EtOH	2	—	—
Benzene	2	5	—
Dioxan	2	32	—
Dioxan	6	17	—
Nitromethane	2	32	—
Nitromethane	6	17	—
Xylene	2	11	20
Chlorobenzene, *o*-dichlorobenzene, trichlorobenzene	2	—	In trace amounts



SCHEME 2

case of **4h**. The optimum yields were obtained with dry dioxan or nitromethane itself as solvent. Under identical conditions, the interaction of **1** with acetonitrile in pyridine did not yield 12-cyano-naphth[2,3-*b*]indolizine-6,11-dione (**4k**); betaine **7** was obtained as the major product. This clearly shows that nitro group is more acid strengthening (pK_a of $CH_3NO_2 = 10.2$) than cyano group (pK_a of $CH_3CN = 25.0$) and hence the resonance stabilization of the nitromethane anion shown in Chart 1 is possible in basic medium provided by pyridine.

In strongly basic medium (e.g. 1 to 1.2 mol of $NaNH_2$ or NaH), the interaction of **1** with acetonitrile did give the desired **4k** in 4% yield. It was identical with an authentic sample prepared by the reported method[8]. The naphthindolizinediones (**4h-4k**, **5d**, **6b**) were crystallized in yellow to orange needles and their structures were in agreement with spectral and elemental data. Their IR and PMR spectra displayed characteristic signals of the naphthindolizinedione ring.

With nitro-substituted naphthindolizinediones in hand, we carried out the reduction of nitro group to obtain appropriate amines. The aminonaphthindolizinediones and their acetyl and benzoyl derivatives enhanced the tinctorial and dyeing properties of these chromophoric systems. (The details about the visible spectral characteristics and dyeing and fastness properties of naphthindolizinediones will be published in a separate communication). Thus, the nitro group of compound **4h** underwent reduction with aq. sodium sulphide to give the corresponding 12-aminonaphth[2,3-*b*]indolizine-6,11-dione (**41**). This compound is reported to be a useful intermediate for various pigments and heterocyclic dyes[9]. The reduction of **4a** and **5a** with aq. sodium sulphide or hydrazine hydrate gave 12-(4′-amino-2′-nitrophenyl)-naphth[2,3-*b*]indolizine-6,11-dione (**4m**) and 14-(4′-

amino-2′-nitrophenyl)benzo[*g*]naphth[2,3-*b*]indolizine-8,13-dione (**5e**) respectively. The selective reduction of 4-nitro group was confirmed by the formation of 2-nitro-*p*-toluidine from DNT under identical conditions. When 12-amino-, 12-(4′-amino-2′-nitrophenyl)naphthindolizinediones and 14-(4′-amino-2′-nitrophenyl)benzo[*g*]naphthindolizinedione (**4l**, **4m** and **5e**), were heated with acetic anhydride, the corresponding monoacetyl derivatives (**4n**, **4o** and **5f**) were obtained in about 90% yields. The acetylation of amino group in 12-(4′-aminophenyl)naphth[2,3-*b*]indolizine-6,11-dione is reported to give a mixture of mono and diacetyl derivatives in 10 and 80% yields respectively[10]. The benzoylation of **4m** gave the benzoyl derivative **4p** in 90% yield. The aminonaphthindolizinediones **4l** and **4m** on treatment with acrylonitrile yielded the N,N-bis-cyanoethyl derivatives **4q** and **4r** respectively in 80% yields. All the aminonaphthindolizinediones and their acetyl, benzoyl and bis-cyanoethyl derivatives were highly coloured (red to violet) crystalline compounds. Their structures were ascertained by spectral data and elemental analyses.

The use of nitromethane and nitrotoluenes thus provides a simple route to nitro and nitroarylnaphthindolizinediones. Although the yields are only moderate in most cases, the procedure is extremely simple and easy to carry out. The dyes obtained by this method give attractive yellow to red dyeings on polyester and show good substantivity and sublimation fastness. Their light fastness, however is only moderate.

Experimental Procedure

All m.ps are uncorrected. UV and visible spectra (λ_{max} in nm and log ε values in parentheses) were recorded in DMF on a Perkin-Elmer 350 spectrophotometer, IR spectra were recorded on a Perkin-Elmer 221 spectrophotometer, PMR spectra on a Varian T-60 spectrophotometer using TMS as internal standard and mass spectra on a CEC-21-110-B mass spectrometer.

12-(2′,4′-*Dinitrophenyl*)*naphth*[2,3-*b*]-*indolizine*-6,11-*dione* (**4a**)

Method-A: *From* 2,3-*dichloro*-1,4-*naphthoquinone* (**1**) *and* 2,4-*dinitrotoluene*

A mixture of **1** (2.27 g), pyridine (3.0 ml) and 2,4-DNT (1.82 g) in dry dioxan (15 ml) was refluxed for 2 hr. The solution turned green, then blue and finally reddish brown. The mixture was cooled and poured onto ice. The reddish-brown solid was filtered, washed with water and dried. The crude product was chromatographed on silica gel using benzene as eluent. The first fraction gave the unreacted **1** (65 mg). The fraction eluted with ethyl acetate-benzene (1:19) gave **4a** (1.3 g, 30%) which recrystallisze from DMF in orange red needles, m.p. 300° (Found: C, 64.3; H, 2.9; N, 10.3. $C_{22}H_{11}N_3O_6$ requires C, 63.9; H, 2.7; N, 10.7%); PMR($AsCl_3$): 9.8 (1H, *d*, $J=7$ Hz, H-4), 9.0 (1H, *d*, $J=2$ Hz, H-3′), 8.85 (1H, *d*, H-5′), 8.6 (1H, *d*, H-6′), 7.25-8.3 (7H, *m*, Ar – *H*); MS: *m/z* 413 (M^+, 100%); UV: 414 (3.6628); 497 (3.8837).

Method-B: *From* 2,4-*dinitrobenzyl bromide*

The synthetic procedure followed was the same as reported earlier for 12-(4′-pyridyl)naphth[2,3-*b*]-indolizine-6,11-dione from 1-(4-pyridylmethyl)pyridinium bromide[4]. The reaction product was chromatographed to give **4a** in 30% yield. It was identical with **4a** prepared above.

Method-C: *From N*-(2-*methoxy*-1,4-*dioxo*-3-*naphthyl*)*pyridinium methosulphate* (**9**)

The methosulphate (**9**) was prepared according to the method reported in the literature[7]. It was heated with equimolar proportions of pyridine and 2,4-DNT in dry dioxan for 2 hr. The reaction mixture on usual work-up as in Method-A gave **4a** in 4% yield. It was identical (superimposable IR and m.m.p.) with **4a** obtained by Methods A and B.

12-(2′,4′,6′-*Trinitrophenyl*)*naphth*-[2,3-*b*]*indolizine*-6,11-*dione* [**4b**; $R_1=2,4,6\text{-}(NO_2)_3.C_6H_2$, $R_2=H$]

Red needles from DMF, m.p. 231° (Found: C, 58.2; H, 2.4; N, 12.0. $C_{22}H_{10}N_4O_3$ requires C, 57.7; H, 2.2; N, 12.2%); PMR($AsCl_3$): 10.05 (1H, *d*, $J=$ Hz, H-4) 9.4 (2H, *s*, H-3′, H-5′), 7.6-8.6 (7H, *m*, Ar – *H*), MS: *m/z* 458 (M^+, 100%); UV: 495 (3.8722).

12-(2′-*Cyano*-4′-*nitrophenyl*)*naphth*[2,3-*b*]-*indolizine*-6,11-*dione* [**4c**; $R_1=2\text{-}(CN)\text{-}4\text{-}(NO_2).C_6H_3$, $R_2=H$]

Red needles from $CHCl_3$, m.p. 307 (Found: C, 69.9; H, 2.7; N, 10.6. $C_{23}H_{11}N_3O_4$ requires C, 72.2; H, 2.8; N, 10.7%); PMR($AsCl_3$): 9.7 (1H, *d*, $J=7$ Hz, H-4) 9.00 (1H, *s*, H-3′), 8.3 (1H, *d*, $J=3$ Hz, H-5′), 8.1 (1H, *d*, $J=2$ Hz, H-6′), 7.1-8.0 (7H, *m*, Ar – *H*); MS: *m/z* 393 (M^+; 100%); UV: 500 (3.8722).

2-*Carbethoxy*-12-(2′-*cyano*-4′-*nitrophenyl*)-*naphth*[2,3-*b*]*indolizine*-6,11-*dione* [**4d**; $R_1=2\text{-}(CN)\text{-}4\text{-}(NO_2).C_6H_3$, $R_2=-COOEt$]

Orange needles from chlorobenzene, m.p. 344° (Found: C, 67.0; H, 3.1; N, 8.9. $C_{26}H_{15}N_3O_6$ requires C, 67.1; H, 3.2; N, 9.00%); UV: 488 (3.8388).

2-*Acetamido*-12-(2′,4′-*dinitrophenyl*)-*naphth*[2,3-*b*]*indolizine*-6,11-*dione* [**4e**; $R_1=2,4\text{-}(NO_2)_2.C_6H_3$, $R_2=-NHCOCH_3$]

1 (2.27 g, 0.01 mol), DNT (1.82 g, 0.01 mol) and 4-acetamidopyridine (5.44 g, 0.01 mol) were interatcted

in dry dioxan (15 ml) as in Method-A (yield 0.225 g, 5%). Dark red needles from chlorobenzene, m.p. >360° (Found: C, 61.2; H, 2.8; N, 11.8. $C_{24}H_{14}N_4O_7$ requires C, 61.3; H, 3.00; N, 11.9%); UV: 537 (3.7160)'.

2-Acetamido-12-(2'-cyano-4'-nitrophenyl)-naphth[2,3-b]indolizine-6,11-dione [**4f**; R_1 = 2-(*CN*)-4-(NO_2)-C_6H_3, $R_2 = -NHCOCH_3$]

Dark red needles from chlorobenzene, m.p. >360° (Found: C, 66.5; H, 3.0; H, 3.0; N, 12.3. $C_{25}H_{14}N_4O_5$ requires C, 66.7; H, 3.1; N, 12.4%); UV: 528 (3.6532).

2-Amino-12-(2'-cyano-4'-nitrophenyl)naphth-[2,3-b]indolizine-6,11-dione [**4g**; R_1 = 2-(*CN*)-4-(NO_2).C_6H_3, $R_2 = -NH_2$]

Violet flakes from chlorobenzene, m.p. >360° (Found: C, 67.5; H, 2.8; N, 13.6. $C_{23}H_{12}N_4O_4$ requires C, 67.6; H, 2.9; N, 13.7%); UV: 440 (3.5911); 557 (3.9294).

12-Nitronaphth[2,3-b]indolizine-6,11-dione [**4h**; $R_1 = NO_2$, $R_2 = H$]

Method-A: From 2,3-dichloro-1,4-naphthoquinone (**1**)

A mixture of **1** (2.77 g, 0.01 mol) and nitromethane (5 ml) in dry dioxan (20 ml) was heated at 80° till a clear yellow solution resulted in. Thereafter, pyridine (3 ml, 0.04 mol) in dry dioxan (5 ml) was added during 20-25 min under stirring when the reaction mixture turned bluish green. The reaction mixture was refluxed further for 2 hr, cooled and poured into ice-water when a reddish orange coloured solid separated out. It was filtered, washed with cold water, dried and chromatographed on silica gel. Elution with benzene gave the unreacted **1** (25 mg). The next fraction eluted with ethyl acetate-benzene (1:19) gave **4h** which crystallized from DMF as yellowish orange needles (0.810 g), 30%, m.p. 266° (lit.[7], m.p. 265°) (Found: C, 65.6; H, 2.5; N, 9.5. Calc. for $C_{16}H_8N_2O_4$: C, 65.8; H, 2.7; N, 9.6%); PMR ($AsCl_3$): 9.7 (1H, *d*, *J* = 7 Hz, H-4), 7.0-8.5 (7H, *m*; Ar − H); MS: *m/z* 292 ($M^{+\cdot}$, 22%); UV: 362 (3.8062); 489 (3.6800).

Method-B: From N-(2-methoxy-1,4-dioxo-3-naphthyl)pyridinium methosulphate (**9**)

A mixture of **9** (3.77 g, 0.01 mol), pyridine (3.0 ml, 0.04 mol) and nitromethane (5.0 ml) was heated in dry dioxan for 2 hr and the reaction mixture worked-up as in method-A to give **4h** (0.500 g, 17%), m.p. 266°, identical with **4h** obtained by method-A.

2-Carbethoxy-12-nitronaphth[2,3-b]indolizine-6,11-dione (**4i**; $R_1 = NO_2$, $R_2 = -COOEt$)

Yellowish orange needles from chlorobenzene, m.p. 321° (Found: C, 62.5; H, 3.2; N, 7.6. $C_{19}H_{12}N_2O_6$ requires C, 62.6; H, 3.3; N, 7.6%); PMR ($AsCl_3$): 9.75 (1H, *d*, *J* = 7 Hz, H-4), 9.3 (1H, *s*, H-1), 7.5-8.7 (5H, *m*, Ar − *H*), 5.0 (2H, *q*, $-CH_2CH_3$), 1.8 (3H, *t*; $CH_3{}^2CH_3$); MS: *m/z* 364 ($M^{+\cdot}$, 17%); UV: 476 (3.8751).

2-Cyano-12-nitronapth[2,3-b]indolizine-6,11-dione (**4j**; $R_1 = NO_2$, $R_2 = N$)

Yellow needles from chlorobenzene, m.p. >360° (Found: C, 66.4; H, 2.3; N, 13.4. $C_{17}H_7N_3O_4$ requires C, 66.4; H, 2.2; N, 13.2%); UV: 474 (3.8195).

12-Cyanonaphth[2,3-b]indolizine-6,11-dione (**4k**; $R_1 = CN$, $R_2 = H$)

Yellowish orange needles from chlorobenzene, m.p. 319° (lit.[7], m.p. 319°) (Found: C, 74.9; H, 3.0; N, 10.4. Calc. for $C_{17}H_8N_2O_2$: C, 75.0; H, 2.9; N, 10.3%); MS: *m/z* 272 ($M^{+\cdot}$, 100%); UV: 352 (3.9031), 476 (3.8325).

12-Aminonaphth[2,3-b]indolizine-6,11-dione (**4l**; $R_1 = NH_2$, $R_2 = H$)

Violet plates from chlorobenzene, m.p. 203° (Found: C, 73.4; H, 3.8; N, 10.8. $C_{16}H_{10}N_2O_2$ requires C, 73.3; H, 3.8; N, 10.7%); UV: 382 (4.1106); 454 (3.6180); 601 (3.7818).

12-(4'-Amino-2'-nitrophenyl)naphth[2,3-b]-indolizine-6,11-dione (**4m**; R_1 = 4-(NH_2)-2-(NO_2)-C_6H_3; $R_2 = H$]

Violet plates from DMF, m.p. 296° (Found: C, 68.8; H, 3.3; N, 10.8. $C_{22}H_{13}N_3O_4$ requires C, 68.8; H, 3.4; N, 11.0%); MS: *m/z* 383 ($M^{+\cdot}$, 37%); UV: 538 (3.7853).

12-Acetaminonaphth[2,3-b]indolizine-6,11-dione (**4n**; $R_1 = -NHCOCH_3$, $R_2 = H$)

A mixture of **4l** (0.525 g, 0.002 mol) and acetic anhydride (3 ml) was refluxed for 30 min. The reaction mixture on cooling gave **4n** (0.490 g, 80%). Orange needles from chlorobenzene, m.p. 265° (Found: C, 70.9; H, 3.8; N, 9.1. $C_{18}H_{12}N_2O_3$ requires C, 71.1; H, 3.9; N, 9.2%); MS: *m/z* 304 ($M^{+\cdot}$, 100%); UV: 488 (3.6946).

12-(4'-Acetamido-2'-nitrophenyl)naphth-[2,3-b]indolizine-6,11-dione [**4o**; R_1 = 4-($NHCOCH_3$)-2-(NO_2).C_6H_3, $R_2 = H$]

Red needles from chlorobenzene, m.p. 280° (Found: C, 67.8; H, 3.6; N, 10.0. $C_{24}H_{15}N_3O_5$ requires C, 67.8; H, 3.5; N, 9.9%); MS: *m/z* 425 (M^+, 55%); UV: 424 (3.5378); 498 (3.7559).

12-(4'-Benzamido-2'-nitrophenyl)naphth-[2,3-b]indolizine-6,11-dione [**4p**; R_1 = 4-($NHCOC_6H_5$)-2-(NO_2).C_6H_3, $R_2 = H$]

Red needles from chlorobenzene, m.p. >360° (Found: C, 71.4; H, 3.4; N, 8.6. $C_{29}H_{17}N_3O_5$ requires C, 71.5; H, 3.5; M, 8.6%).

12-(*Bis-cyanoethylamino*)*naphth*[2,3-*b*]-*indolizine*-6,11-*dione* [**4q**; $R_1 = -N(CH_2CH_2CN)_2$, $R_2 = H$]

The compound **4l** (0.525 g, 0.002 mol) was reacted with excess acrylonitrile (5 ml) and copper acetate dissolved in acetic acid. The mixture was refluxed for 30 min, cooled and poured into ice-cold water. The bis-cyanoethyl derivative (**4q**) was purified by crystallization (0.580 g, 80%). Red needles from chlorobenzene, m.p. >360° (Found: C, 71.6; H, 4.3; N, 15.1. $C_{22}H_{16}N_4O_4$ requires C, 71.7; H, 4.3; N, 15.2%); UV: 493 (3.8808).

12-(*Bis-cyanoethylamino*)-2′-*nitro*-4′-*phenyl*-*naphth*[2,3-*b*]*indolizine*-6,11-*dione* [**4r**; $R_1 = 4$-$N(CH_2CH_2CN_2)$-2-$(NO_2).C_6H_3$, $R_2 = H$]

Red needles from chlorobenzene, m.p. >360° (Found: C, 68.6; H, 3.8; N, 14.3. $C_{28}H_{19}N_5O_4$ requires C, 68.7; H, 3.9; N, 14.3%); UV: 516 (4.0000).

14-(2′,4′-*Dinitrophenyl*)*benzo*[*g*]*naphth*-[2,3-*b*]*indolizine*-8,13-*dione* [**5a**; $R_1 = 2,4$-$(NO_2)_2.C_6H_3$]

Orange needles from DMF, m.p. 324° (Found: C, 67.7; H, 3.0; N, 8.9. $C_{26}H_{13}N_3O_6$ requires C, 67.4; H, 2.8; N, 9.1%); PMR($AsCl_3$): 9.8 (1H, *d*, $J = 7$ Hz, H-6), 9.4 (1H, *d*, $J = 2$ Hz, H-3), 9.0 (1H, *d*, $J = 3$ Hz, H-5′), 8.85 (1H, *d*, $J = 2$ Hz, H-6′), 7.6-8.55 (9H, *m*, Ar−*H*); MS: *m/z* 463 ($M^{+\cdot}$, 39%); UV: 468 (3.8976).

14-(2′,4′,6′-*Trinitrophenyl*)*benzo*[*g*]-*naphth*[2,3-*b*]*indolizine*-8,13-*dione* [**5b**; $R_1 = 2,4,6$-$(NO_2)_3.C_6H_2$]

Yellowish orange needles from DMF, m.p. >360° (Found: C, 61.3; H, 2.2; N, 10.9. $C_{26}H_{12}N_4O_8$ requires C, 61.4; H, 2.4; N, 11.00%); PMR ($AsCl_3$): 9.75 (1H, *d*, $J = 7$ Hz, H-6), 8.4 (2H, *s*, H-3′, H-5′), 7.4-8.3 (9H, *m*, Ar-*H*); UV: 462 (3.7853).

14-(2′-*Cyano*-4′-*nitrophenyl*)*benzo*[*g*]-*naphth*[2,3-*b*]*indolizine*-8,13-*dione* [**5c**; $R_1 = 2$-(CN)-4-(NO_2)-C_6H_3]

Orange needles from DMF, m.p. 360° (Found: C, 73.0; H, 2.8; N, 9.3. $C_{27}H_{13}N_3O_4$ requires C, 73.1; H, 2.9; N, 9.5%); PMR($AsCl_3$): 9.5 (1H, *d*, $J = 7$ Hz, H-6), 9.00 (1H, *s*, H-3′), 8.2 (1H, *d*, $J = 2$ Hz, H-5′), 8.1 (1H, *d*, $J = 3$ Hz, H-6′), 7.00-8.00 (9H, *m*, Ar-*H*); UV: 454 (3.6990).

14-*Nitrobenzo*[*g*]*naphth*[2,3-*b*]*indolizine*-8,13-*dione* (**5d**; $R_1 = NO_2$)

Orange needles from chlorobenzene, m.p. 336° (Found: C, 70.2; H, 3.4; N, 8.0. $C_{20}H_{10}N_2O_4$ requires C, 70.3; H, 3.4; N, 8.2%); PMR($AsCl_3$): 9.6 (1H, *d*, $J = 7$ Hz, H-6), 7.3-8.6 (9H, *m*, Ar-*H*); MS: *m/e* 342 (M^+, 25%); UV: 467 (3.8633).

14-(4′-*Amino*-2′-*nitrophenyl*)*benzo*[*g*]*naphth*-[2,3-*b*]*indolizine*-8,13-*dione* [**5e**; $R_1 = 4$-(NH_2)-2-$(NO_2).C_6H_3$]

Reddish violet plates from nitrobenzene, m.p. >360° (Found: C, 71.9; H, 3.4; N, 9.6. $C_{26}H_{15}N_3O_4$ requires C, 72.1; H, 3.5; N, 9.7%); UV: 530 (3.6532).

14-(4′-*Acetamido*-2′-*nitrophenyl*)*benzo*-[*g*]*naphth*[2,3-*b*]*indolizine*-8,13-*dione* [**5f**; $R_1 = 4$-$(NHCOCH_3)$-2-$(NO_2).C_6H_3$]

Red needles from chlorobenzene, m.p. >360° (Found: C, 70.6; H, 3.5; N, 8.7. $C_{28}H_{17}N_3O_5$ requires C, 70.7; H, 3.6; N, 8.8%).

7-(2′,4′-*Dinitrophenyl*)*benz*[5,6]-*indolo*[1,2-*a*]*quinoline*-8,13-*dione* [**6a**; $R_1 = 2,4$-$(NO_2)_2.C_6H_3$]

Yellowish orange needles from DMF, m.p. 336° (Found: C, 67.3; H, 2.7; N, 8.9. $C_{26}H_{13}N_3O_6$ requires C, 67.4; H, 2.8; N, 9.1%); PMR($AsCl_3$): 9.6 (1H, *d*, $J = 7$ Hz, H-6), 9.2 (1H, *s*, H-3′), 8.6-8.7 (2H, *m*, H-5′, H-6′), 7.4-8.3 (9H, *m*, Ar-*H*); MS: *m/z* 463 ($M^{+\cdot}$, 36%); UV: 472 (3.9294).

7-*Nitrobenz*[5,6]*indolo*[1,2-*a*]-*quinoline*-8,13-*dione* (**6b**; $R_1 = NO_2$)

Orange needles from DMF, m.p. 304° (Found: C, 70.1; H, 3.5; N, 8.3. $C_{20}H_{10}N_2O_4$ requires C, 70.3; H, 3.4; N, 8.2%); PMR($AsCl_3$): 9.6 (1H, *d*, $J = 7$ Hz, H-6), 7.6-8.5 (9H, *m*, Ar-*H*); MS: *m/z* 342 ($M^{+\cdot}$, 12%); UV: 464 (3.9845).

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Studies on β-Enaminonitriles: Part I—Benzoylation in Presence of Sodium in Benzene†‡

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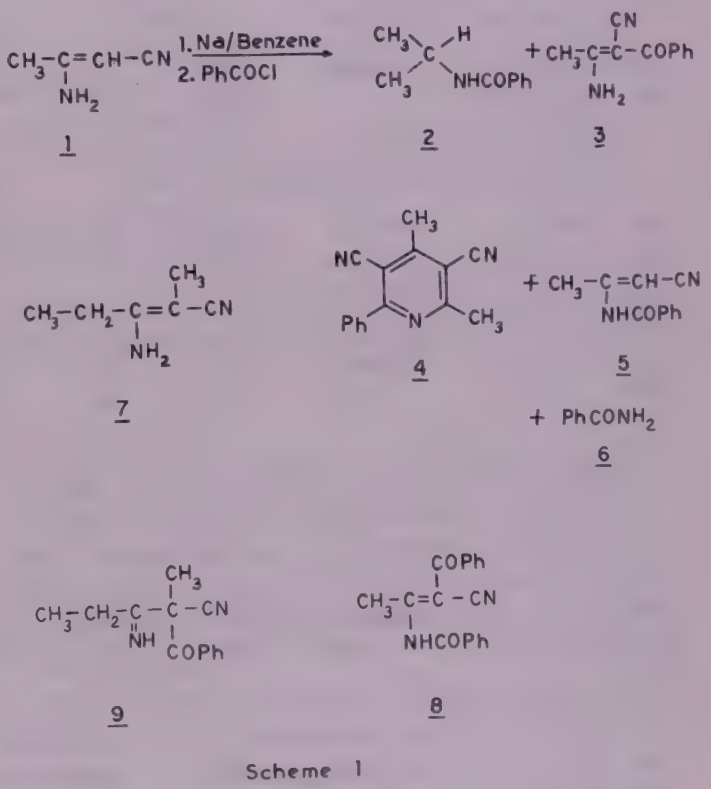
Sodium dust in benzene brings about an unusual reductive decyanation of β-aminocrotononitrile (**1**) to afford N-benzoylisopropylamine (**2**) as the major product, for which a tentative mechanism involving radical addition has been suggested. Benzoylation of β-aryl-β-aminoacrylonitriles (**10**, **11** and **12**), however, under similar conditions furnish a complex mixture of compounds, namely, β-aryl-β-amino-α-benzoylacrylonitriles (**14**, **18** and **22**), pyrimidines (**13**, **17** and **21**), β-ketonitriles (**19**, **20** and **23**) and benzamide (**16**) in varying yields but in no case the formation of the corresponding reductive decyanation products have been observed.

Ever since the pioneering work of Stork[1] on the reactivity of enamines, the growth of literature in this area has been exponential[2a–d]. However, not much information is available on the chemistry of primary enaminonitriles and the area seems largely unexplored. This prompted us to undertake the title investigation to seek a method for a straightforward synthesis of 4-substituted isothiazoles via the corresponding C-acylated or C-alkylated enaminonitriles. Recently[3], we have worked out a highly successful method to achieve complete regioselectivity in the acylation reactions of β-enaminonitriles in the presence of an added organic base. As a consequence to these observations, it appeared to be interesting to see if such regioselectivity is also operative in the case of acylation carried under anionic conditions. Herein, we report our findings on the acylation of aliphatic and aromatic enaminonitriles in the presence of sodium in benzene.

β-Aminocrotononitrile (**1**) (1.64 g, 0.02 mol) was treated with sodium dust (0.46 g, 0.02 mol) in dry benzene (20 ml) at 0°C and left overnight at room temperature. The solid cake thus obtained was then reacted with benzoyl chloride (2.91 g, 0.02 mol) at 0°C and the reaction mixture was allowed to attain ambient temperature. Usual work-up provided a viscous gummy material which on extensive chromatography over silica gel afforded a mixture of products (Scheme 1, Table 1). The structural elucidation of the products were based on elemental analysis and UV, IR, PMR and mass spectra. N-Benzoyl derivative of isopropylamine (**2**) was obtained as the major product. The structural assignment of **2** was confirmed by comparison with an authentic sample[4]. The formation of **2** in this reaction clearly indicates that during the course of the reaction reductive cleavage of the nitrile group had occurred. This novel reductive decyanation of **1**, to the best of our knowledge, has not yet been reported in the literature.



Scheme 1

Elimination of benzylic cyano group on Birch reduction[5] and reductive decyanation of α-cyanocarbanions in the presence of alkali metals in HMPT[6] have been reported. Adkins and Whitman[7] isolated isopropylamine as one of the products of hydrogenation with aliphatic enaminonitriles. The role of sodium dust used for salt formation in this reaction needed a careful examination. That sodium dust is actually responsible for such unusual reductive

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‡Abstracted in part from the PhD thesis of M Sarkar, Jadavpur University, April 1984.

Table 1—Characterisation Data of Compounds (2, 3-5, 8, 9, 13-15, 17-23)

Compd[a] (Yield mg)	m.p. °C	Eluent[b]	Found (Calc.) % C	H	N	Spectral data
2 (600)	102-103 (lit.[4] 100-101)	Benzene -Pet ether (3:2)	73.7 (73.6	7.9 7.9	8.6 8.6)	IR : 3440, 1650[d] PMR : 1.16 and 1.26 (*s*, 6H, CH_3); 4.00-4.40 (*m*, 1H, $(CH_3)_2CH-$); 6.66-7.00 (*br*, 1H, *NH*); 7.16-7.43 (*m*, 3H, Ar-*H*), 7.66-7.86 (*m*, 2H, Ar-*H*)[c] MS : *m/z* 163 (M^+)
3 (150)	147-48 (lit.[8] 148)	Chloroform -Benzene (4:1)	70.9 (71.0	5.4 5.8	15.2 15.1)	IR : 3300, 3120, 2000[e] PMR : 2.33 (*s*, 3H, CH_3); 7.33-7.60 (*m*, 3H, Ar-*H*); 7.60-7.86 (*m*, 2H, Ar-*H*); 6.61 and 10.25 ($-NH_2$)[c] MS : *m/z* 186 (M^+)
4 (20)	141-42	Benzene -Pet ether (1:1)	77.1 (77.3	4.8 4.7	17.8 18.0)	IR : 2240, 1400[e] PMR : 2.84 and 2.88 ($2\times s$, 6H, $2\times CH_3$); 7.50-7.66 (*m*, 3H, Ar-*H*); 7.88-8.04 (*m*, 2H, Ar-*H*)[b] MS : *m/z* 233 (M^+)
5 (50)	78-79 (lit.[9] 80-81)	Benzene	80.1 (80.0	5.4 5.4	14.8 15.1)	IR : 3480, 1710[d] PMR : 2.28 (*d*, $J=0.88$ Hz, 3H, CH_3); 6.56 (*d*, $J=0.88$ Hz, 1H, $-CH-CN$); 6.25-6.46 (*br*, 1H, N*H*)[c], 7.56-7.66 (Ar-*H*)[c] MS : *m/z* 186 (M^+)
8 (500)	154-55 (lit.[10] 158)	Benzene -Pet. ether (1:1)	74.2 (74.5	4.7 4.8	9.4 9.7)	IR : 3160, 2200, 1708[e] PMR : 3.05 (*s*, 3H, $CH_3-C=$); 7.30-7.70 (*m*, 6H, Ar-*H*); 7.60-8.10 (*m*, 4H, Ar-*H*)[c] MS : *m/z* 290 (M^+)
9 (250)	189-90	Benzene	72.7 (72.9	6.3 6.5	12.9 13.1)	IR : 3290, 2220, 1705[f] PMR : 1.61 (*t* $J=8$ Hz, 3H, CH_3CH_2-); 1.92 (*s*, 3H, CH_3-C-CN); 2.98 (*q*, $J=8$ Hz, 2H, CH_3-CH_2-); 7.36-7.76 (*m*, 3H, Ar-*H*); 7.80-8.04 (*m*, 2H, Ar-*H*); 9.65 (*s*, 1H, $=N-H$)[c] MS : *m/z* 214 (M^+)
13 (30.6)	255 (lit.[11] 255)	Benzene -Pet ether (2:3)	82.6 (82.9	4.6 4.5	12.7 12.6)	IR : 2220, 1485 UV : 273 (39, 041)[g] PMR : 7.48-7.72 (*m*, 9H, Ar-*H*); 8.08-8.32 (*m*, 4H, Ar-*H*); 8.64-8.80 (*m*, 2H, Ar-*H*) MS : *m/z* 333 (M^+)
14 (224)	214-15 (lit.[12] 213)	Chloroform -Benzene (1:4)	77.4 (77.4	4.7 4.8	10.8 11.3)	IR : 3290, 3130, 2200 UV : 243 (8, 184), 321 (11, 904) PMR : 7.32-7.94 (*m*, 10H, Ar-*H*); 6.35, 10.5 (*s*, 2H, $-NH_2$)[h] MS : *m/z* 284 (M^+)
15 (238)	263-64 (lit.[13] 263-70)	Chloroform	83.4 (83.6	4.7 4.7	11.6 11.7)	IR : 2199, 2208, 1635 PMR : 4.69 (*s*, 1H, *HC*-Ph); 7.46-7.57 (*m*, 5H, Ar-*H*)[h] MS : *m/z* 359 (M^+)
17 (51.7)	239-40	Benzene -pet ether (1:9)	68.3 (68.5	3.2 3.2	10.5 10.4)	IR : 2220, 1590[d] PMR : 7.48-7.76 (*m*, 7H, Ar-*H*); 8.16 (*m*, 4H, Ar-*H*); 8.64 (*m*, Ar-*H*) MS : *m/z* 402 (M^+) 403 (M+1)
18 (130)	220-22	Benzene	68.1 (68.0	3.7 3.9	9.8 9.9)	IR : 3320, 3100, 2198 UV : 215 (1220), 245 (904), 320 (1130) PMR : 7.43-7.81 (*m*, 9H, Ar-*H*); 6.42, 10.46 (*s*, 2H, $-NH_2$) MS : *m/z* 282 (M^+)
19	124	Benzene	60.0	3.4	8.2	IR : 2265, 1705[d] PMR : 4.03 (*s*, 2H, $-CH_2-$); 7.50 (*d*, 2H, $J=8$ Hz, Ar-*H*);

(*Contd*)

Table 1—Characterisation Data of Compounds (2, 3-5, 8, 9, 13-15, 17-23) —*Contd*

Compd[a] (Yield mg)	m.p. °C	Eluent[b]	Found (Calc.) % C	H	N	Spectral data
(128)	(lit.[14] 127)	-Pet ether (3:7)	(60.1	3.3	7.8)	7.88 (*d*, 2H, *J*=8 Hz, Ar-*H*); MS : *m/z* 179 (M^+); IR : 2220, 1710[d]
20 (207)	180-81	Benzene -Pet ether (1:1)	67.5 (67.7	3.4 3.5	4.5 4.9)	PMR : 7.44-7.84 (*m*, 3H, Ar-*H*); 7.88-8.24 (*m*, 6H, Ar-*H*); 14.08 (*s*, 1H, −O*H*) MS : *m/z* 283 (M^+) 284 (M+1); IR : 2220, 1580[d]; UV : 315, (40, 610)[h]
21 (72.5)	170-71	Benzene -Pet ether (2:3)	76.3 (76.2	4.7 4.8	10.5 10.7)	PMR : 3.88 and 3.90 (2×*s*, 6H, 2×−OCH_3); 7.08 (*m*, 3H, Ar-*H*); 7.46 (*m*, 4H, Ar-*H*); 8.40 (*m*, 4H, Ar-*H*); 8.70 (*m*, 2H, Ar-*H*) MS : *m/z* 393 (M^+); IR : 3280, 3104, 2220; UV : 223 (9, 911), 328 (16, 800)
22 (725)	231-32	Benzene -Chloroform (19:1)	73.1 (73.4	4.8 5.0	10.2 10.1)	PMR : 3.84 (*s*, 3H, −OCH_3); 7.10 (*d*, *J*=8 Hz, 2H, Ar-*H*); 7.60 (*d*, *J*=8 Hz, 2H, Ar-*H*); 7.80 (*m*, 5H, Ar-*H*); 6.38, 10.46 (*s*, 2H, −NH_2)[h] MS : *m/z* 278 (M^+); IR : 2260, 1690
23	128 (lit.[15] 132)	Benzene -Pet ether (3:4)	68.2 (68.6	5.2 5.1	8.1 8.0)	PMR : 3.90 (*s*, 3H, −OCH_3), 3.98 (*s*, 2H, CH_2−CN); 6.96 (*d*, *J*=8 Hz, 2H, Ar-*H*); 7.90 (*d*, *J*=8 Hz, 2H, Ar-*H*) MS : *m/z* 175 (M^+)

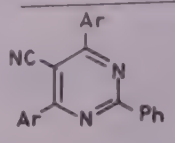
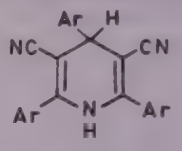
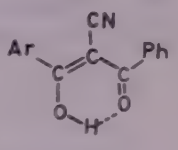
(a) Numbers refer to compound depicted in Scheme 1 and Table 2. These compounds were separated by column chromatography over silica gel (BDH, 60-120 mesh) (b) Pet. ether refers to fraction b.p. 60-80°C (c) $CDCl_3$; (d) chloroform; (e) Nujol mull; (f) KBr-pellet; (g) acetonitrile and (h) DMSO-d_6.

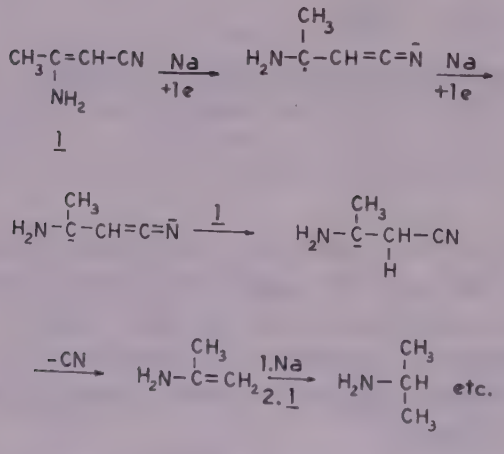
decyanation of **1** comes from the observation that when benzoylation of β-aminocrotononitrile (**1**) was carried out in the presence of sodium hydride in benzene, C,N-dibenzoylated β-aminocrotononitrile (**8**) was obtained as the sole product. From these experiments it is quite clear that the presence of metallic sodium is a necessity to bring about such a reductive decyanation. In order to explore the generality of this reaction we have also studied benzoylationof different aromatic β-enaminonitriles (Table 2). It is highly pertinent to note that no such reductive decyanation was observed in any of these cases. It appears that this type of cleavage is only associated with β-aminocrotononitrile (**1**) as compound **7** failed to undergo reductive decyanation under the same experimental conditions, the major product isolated being the corresponding C-acylated derivative **9** along with a trace quantity of benzamide.

A likely pathway for the formation of isopropylamine via reductive decyanation of **1** has been suggested (Scheme 2). The protonation of the intermediate dianion can also the place at β-carbon atom leading to the formation of crotononitrile or derived products by elimination of ammonia. These products are volatile as well as water soluble and if formed at all, could very well remain undetected during work-up. This postulation is largely based on the characterisation of isolated materials thus supporting the suggestion of protonation at α-carbon atom. Further mechanistic studies in this direction are under progress.

Benzoylation reactions with the sodium salts of different β-aryl-β-aminoacrylonitriles (**10-12**) were complex in nature and only on exhaustive chromatography (silica gel) the products β-aryl-β-amino-α-benzoylacrylonitriles (**14**, **18** and **22**), pyrimidines (**13**, **17** and **21**), β-ketonitriles (**19**, **20** and **23**) and benzamide (**16**) in varying yields could be isolated of which α-benzoylated products were found to be the major ones (Table 2). These reaction were repeated on quite a few occasions but the yields of the products were found to be variable. The structure of the compounds were confirmed through elemental and spectroscopic analyses (Table 1). These reactions are found to be synthetically of little interest because of complexity of reaction products. A notable feature of all these reactions is the complete absence of products resulting from reduction decyanation of the corresponding enaminonitriles as found to be associated with β-aminocrotononitrile (*loc. cit.*).

Table 2 — Acylation Of β - Enaminonitriles (10, 11, 12) With Benzoyl Chloride

Entry	Starting Material	Products			
	Ar-C(NH$_2$)=CH-CN (Ar)		Ar-C(NH$_2$)=C(CN)COPh	Others	
1	Ph (10)	13	14	 15	$PhCONH_2$ 16
2	p-ClC$_6$H$_4$ (11)	17	18	Ar-C(=O)-CH$_2$CN 19	Ar-C(=O)-CH(CN)COPh ⇌  20
3	p-MeOC$_6$H$_4$ (12)	21	22	Ar-C(=O)-CH$_2$CN 23	$PhCONH_2$ 16



Scheme 2

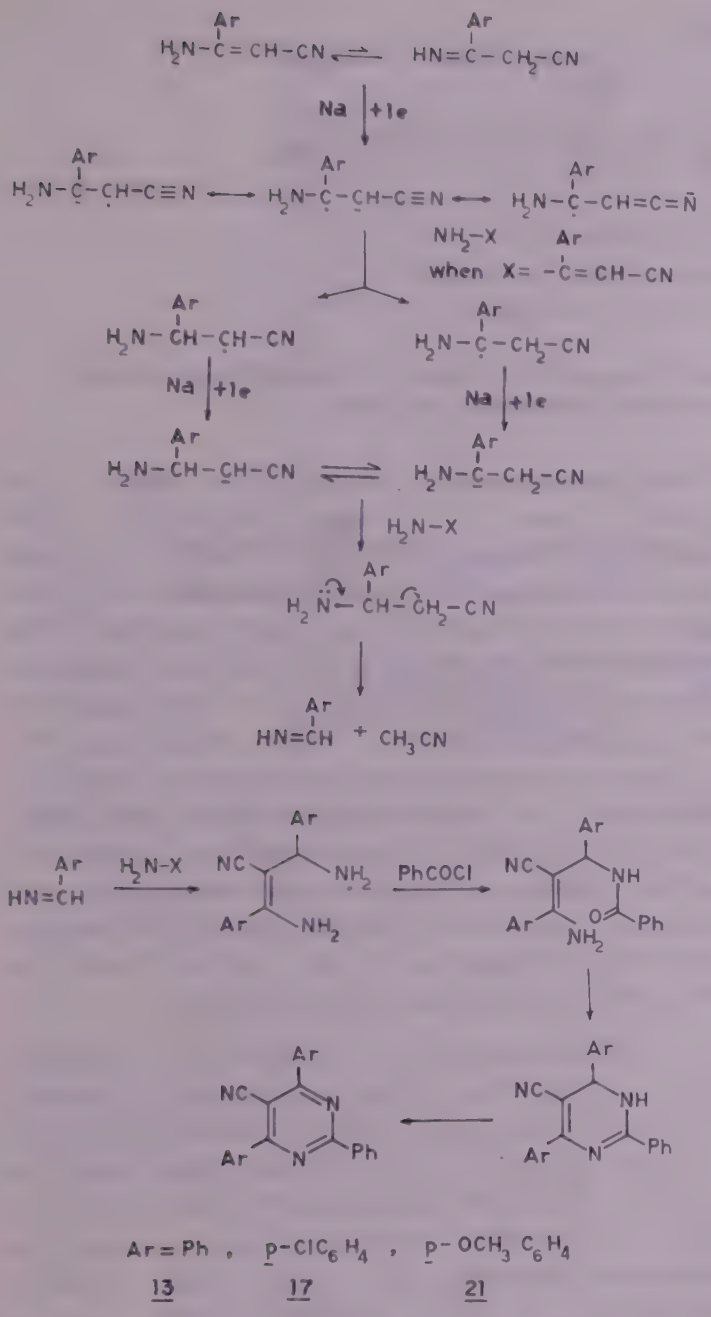
Examination of Table 2 points to the following observations: (i) Though the reaction is of complex nature, the products isolated result mostly from C-benzoylation. (ii) The complex nature of the reaction mixture could be due to the presence of sodium which may induce cleavage of the enaminonitrile by radical addition process. The formation of pyrimidine derivatives (**13**, **17** and **21**) may be ascribed to this phenomenon (Scheme 3). (iii) Except entry 2 (Table 2), in all other cases, trace quantity of benzamide was isolated, resulting probably from the hydrolysis of N-benzoylated products. In the case of entry 1 (Table 2) 1,4-dihydropyridine (**15**) was islated as the major product. The mechanistic aspects for the formation of this products is being investigated. As benzoylation of β-aryl-β-aminoacrylonitriles in the presence of sodium in benzene afforded a complex mixture of products due to the intervention of a radical process it is expected that benzoylation, in presence of sodium hydride, should prevent formation of undesirable products. Currently we are persuing these studies.

Experimental Procedure

All melting points were determined in open capillaries and are uncorrected. UV spectra (ν_{max} in nm, ε in parentheses) in ethanol, unless specified otherwise, were taken on a Perkin-Elmer-Hitachi spectrophotometer model 200. IR spectra (ν_{max} in cm^{-1}) in nujol mull, unless specified otherwise, were recorded on Perkin-Elmer 297 spectrophotometer. The PMR spectra were run on a Bruker WP 80, Jeol FX 100 and Varian 60T instruments in $CDCl_3$, unless specified otherwise, using TMS as an internal standard; chemicals shifts are expressed in δ scale. Mass spectra were recorded on a Hitachi RMU 6L instrument. Silica gel (BDH, 60-120 mesh) was used for column chromatography.

Reaction of sodio-salt of β-aryl-β-aminoacrylonitrile with benzoyl chloride: General procedure

To a stirred suspension of sodium dust (0.01 mol) in dry benzene (20 ml) was added dropwise a solution of β-aryl-β-aminoacrylonitrile (0.01 mol) in dry benzene (40 ml) at 0°C. It was warmed for 2 hr at 60-70°C and cooled to 0°C. To this was dropwise with stirring a solution of benzoyl chloride (0.01 mol) in dry benzene (15 ml) at 0°C and the reaction mixture was kept



Ar = Ph , p-ClC$_6$H$_4$, p-OCH$_3$C$_6$H$_4$

13 17 21

Scheme 3

overnight to attain ambient temperature. Usual work-up afforded a brownish yellow mass. Exhaustive column chromatography using eluent mixture in Table 1 yielded the products.

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Synthesis of Tuftsin Using Picolyl Ester Method

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A convenient and quick synthesis of tuftsin, a immuno-modulating tetrapeptide is reported. The intermediates are isolated and characterised as picolyl ester derivatives. The synthetic tetrapeptide is found to be fully active.

Tuftsin[1], a naturally occurring tetrapeptide, is an integral part of immunoglobulin Ig, which only when liberated from the parent molecule exhibits strong immunopotentiating activities[2,3]. Tuftsin administered *in vitro* modulates humoral and cell mediated immune functions. It increases the phagocytosis in *PMNL* and macrophages, stimulates the cell motility[4,5] and augments antigen specific macrophage dependent sensitisation of lymphocytes[6]. Tuftsin activation of macrophage also results in increased cytostatic and ctyotoxic activities towards bacteria and syngeneic tumor cells[7]. Recent experiments suggest that tuftsin has antitumor activity against murine tumors[8].

In order to evaluate the potential of tuftsin as immuno-modulator in certain cancer and leprosy conditions we required relatively large amount of this tetrapeptide. Tuftsin and its numerous analogues have been synthesised[9] by many groups using both solution and solid phase techniques of peptide synthesis. Following these published protocols, however, we experienced some difficulties in isolation and purification of the intermediates and the final products which resulted in low overall yields. In this paper we wish to report a convenient, quick and high yielding synthesis of tuftsin using picolyl ester method of peptide synthesis, first developed by Young and coworkers[10]. This method involves the incorporation of weakly basic picolyl group at the C-terminus as ester of relevant amino acid. Peptide couplings are usually mediated by dicyclohexylcarbodiimide (DCC)/N-hydroxybenztriazole or active esters.

The growing peptide has slight basic character due to picolyl group and can either be extracted into aqueous solution leaving behind the impurities which are generally neutral or acidic, or separated by using an ion exchange column. For small peptides, extraction into aqueous citric acid solution has been found most suitable, which is also compatible with *t*-butoxycarbonyl group, the most commonly used amino protection group in peptide synthesis.

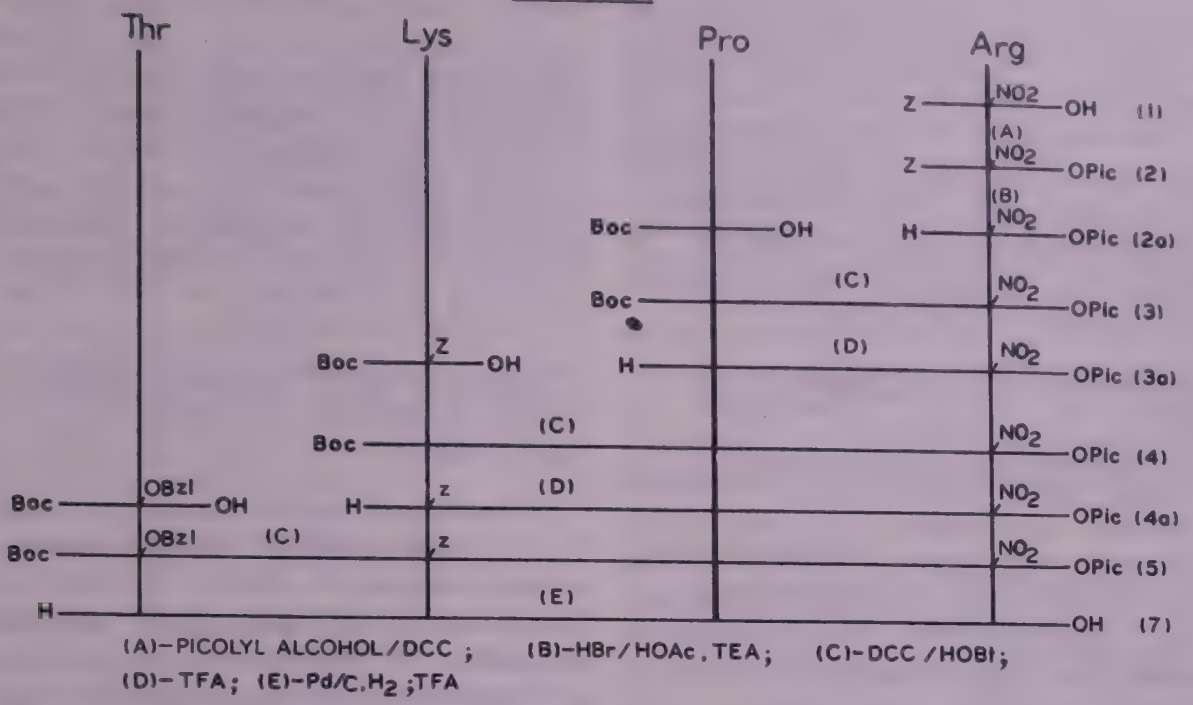
For the synthesis of tuftsin (**7**) (see Scheme 1) the picolyl ester (**2**) was prepared from benzyloxycarbonylnitro-L-arginine using DCC and picolyl alcohol in 74.0% yield. Treatment of **2** with anhydrous hydrogen bromide in acetic acid led to the removal of carbobenzoxy group. The resulting product was then coupled with 1.3 molar excess of *t*-butoxycarbonyl-L-proline, using DCC and N-hydroxybenztriazole. Isolation by aqueous citric acid procedure[9] gave chloromatographically pure dipeptide (**3**) in 85% yield. The dipeptide (**3**) was deprotected with anhydrous trifluoroacetic acid and coupled with 1.4 molar excess of N^{α}-*t*-butyloxycarbonyl-N^{ε}-benzyloxycarbonyl-L-lysine as in the case of **3** and the tripeptide (**4**) was isolated in 90% yield.

For the introduction of threonine, the C-terminal amino acid in tuftsin, N-butyloxycarbonyl-O-benzyl-L-threonine was coupled with N-terminal deprotected tripeptide using DCC and N-hydroxybenztriazole to give fully protected tetrapeptide (**5**) in 82% yield. For primarily economic reasons, we also attempted to introduce threonine with side chain hydroxyl unprotected, but DCC mediated coupling gave a number of products. However, active ester coupling with the tripeptide (**4**) gave satisfactory results. Thus tripeptide (**4**) was treated with the anhydrouns trifluoroacetic acid in dichloromethane (1:1) and the trifluoroacetate salt was coupled with benzyloxycarbonyl-L-threonine pentachlorophenyl ester to yield the tetrapeptide (**6**) in 85% yield (Scheme 2).

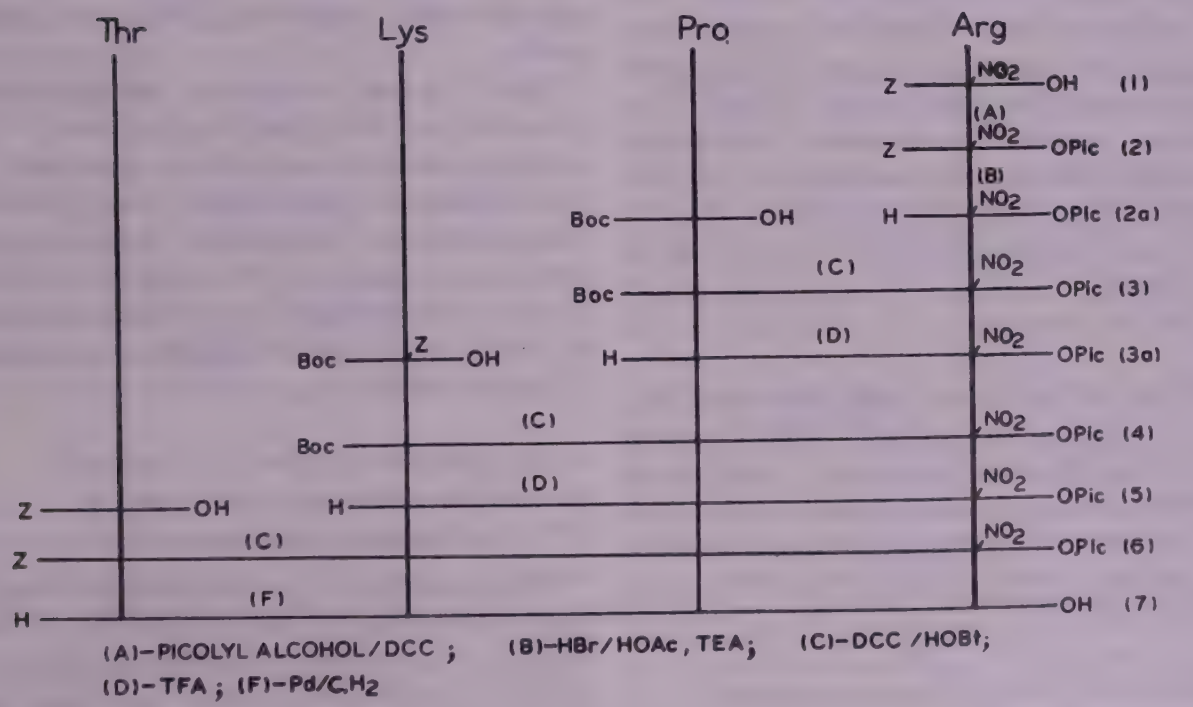
Hydrogenation of **6** over 10% Pd/C removed all the protecting groups and tuftsin (**7**) was isolated as a colourless fluffy solid in 53% yield.

Protected tetrapeptide (**5**) was first deprotected by hydrogenation over 10% Pd/C followed by treatment with trifluoroacetic acid to afford **7**. The synthetic tetrapeptide (**7**) obtained by both the methods showed similar physicochemical properties and full bioactivity. All the intermediate peptides were chromatographically pure, gave satisfactory elemental analyses

SCHEME 1



SCHEME 2



and their PMR spectra were compatible with the assigned structures.

Experimental Procedure

Amino acids (Sigma Chemicals Co.) were used as such. All solvents were purified in the laboratory according to the established procedures. Dimethylformamide, used as the coupling solvent, was purified and dried by the method of Thomas and co-workers[11].

Melting points were taken on a Kofler hot bench melting point apparatus and are uncorrected. 90 MHz Perkin-Elmer R-32 spectrometer was used for PMR spectra with TMS as an internal reference. Optical rotations were taken on JASCO Dip-360 polarimeter.

Thin layer chromatography was performed on silica gel plates using the following solvent systems: (A) $CHCl_3 - CH_3OH$ (9:1), (B) *n*-BuOH-AcOH-H_2O (4:1:1), (C) EtOAc (3 vol) and pyridine-AcOH-H_2O (20:6:11) (1 vol) and (D) *n*-BuOH-Pyridine-AcOH-H_2O (16:10:3:12).

The thin layer plates were visualised with iodine vapours, 1% ninhydrin in acetone and/or Cl_2-KI-starch reagent.

N^{α}-benzyloxycarbonyl-N^{ω}-nitro-L-arginine (1) was

prepared[11] on 50 mmol scale in 61% yield, m.p. 252° (lit.[12] m.p. 252-56°). *t*-Butyloxycarbonyl-L-proline was prepared[13] from L-proline using di-*t*-butyldicarbonate on 10 mmol) scale in 64% yield, m.p. 135° (lit.[12] m.p. 135°). N^{α}-*t*-Butoxycarbonyl-N^{ε}-benzyloxycarbonyl-L-lysine was prepared[15] starting from L-lysine on 0.1 mol scale in 72% overall yield. N-Benzyloxycarbonyl-L-threonine pentachlorophenyl ester was prepared[16] in 90% yield; m.p. 196°. *t*-Butyloxycarbonyl-O-benzyl-L-threonine was purchased from Sigma Chemicals.

N^{α}-Benzyloxycarbonyl-N^{ε}-nitro-L-arginine-4-picolyl ester[16] (**2**)

N^{α}-Benzyloxycarbonyl-N^{ε}-nitro-L-arginine (9.2 g, 2.5 mmol) and picolyl alcohol (2.8 g, 2.0 mmol) dissolved in DMF, were stirred in an ice bath. DCC (5.15 g, 2.5 mmol) was added in portions during 30 min. and further stirred for 2 hr. Ethylacetate (25 ml) was added at 0°C. The precipitated dicyclohexylurea was filtered off and washed with cold ethyl acetate. The filtrate and washings were combined, evaporated, the residue taken up in hydrochloric acid (2 *M*, 250 ml) and washed with EtOAc (2 × 20 ml), ether (2 × 30 ml). The solution was made alkaline with solid $NaHCO_3$ and the liberated solid was extracted into ethyl acetate (500 ml). The organic extract was washed with water (50 ml), brine (50 ml), dried (Na_2SO_4) and evaporated to yield the ester (**2**) as colourless solid (8.5 g, 74%), m.p. 152-53°. R_f (A) 0.3; R_f (B) 0.6; R_f (C) 0.45; $[\alpha]_D^{20}$ −13.4 (*c*, 1.0, in DMF) (Found: C, 52.2; H, 5.7; N, 18.3. $C_{20}H_{25}N_6O_6.H_2O$ requires C, 51.8; H, 5.8; N, 18.1%).

N^{ω}-Nitro-L-arginine picolyl ester dihydrobromide (**2a**)

Ester (**2**, 7 g) was treated with HBr (5 ml) in anhydrous acetic acid for 15 min. at 0°C and then at room temperature for 15 min. Excess reagent was removed *in vacuo* and the residue triturated with dry ether to give **2a** as a white hygroscopic solid (6.9 g, 93% yield); R_f (B) 0.12.

t-Butoxycarbonyl-L-prolyl-N^{ω}-nitro-L-arginine-4-picolyl ester (**3**)

t-Butoxycarbonyl-L-proline (2.8 g, 13 mmol), 1-hydroxybenztriazole (1.75 g, 13 mmol) and DCC (2.5 g, 13 mmol) in DMF (25 ml) were stirred together at 0°C. To this was added a solution of **2a** (4.87 g, 10 mmol) and triethylamine (2.7 ml, 20 mmol) in dimethylformamide at 0°C and the mixture stirred for 12 hr at room temperature. The mixture was then stirred for 30 min with ethyl acetate (20 ml) at 0°C and the precipitated dicyclohexylurea filtered. Solvent was removed *in vacuo* and the residue dissolved in ethyl acetate-ether (1:1, 30 ml) was extracted with 0.7 *M* citric acid solution (4 × 20 ml). The citric acid extracts were combined, and washed with ether unitl no impurity was extracted. The aqueous phase was made alkaline with solid $NaHCO_3$ and the liberated oily product extracted into ethyl acetate (5 × 20 ml). The organic phase was washed with brine (1 × 30 ml), dried (Na_2SO_4) and evaporated *in vacuo* to give **3** a colourless fluffy solid (4.5 g) in 85.1% yield, m.p. 97°, $[\alpha]_D^{20}$ −38.3 (*c*, 1.0, in DMF); R_f (B) 0.49, R_f (C) 0.35 (Found: C, 51.6; H, 6.8; N, 19.2. $C_{22}H_{34}N_7O_7$ requires C, 51.9; H, 6.7; N, 19.3%).

N^{α}-Butoxycarbonyl-N^{ε}-benzyloxycarbonyl-L-lysyl-L-prolyl-N^{ω}-nitro-L-arginine picolyl ester (**4**)

N -Butoxycarbonyl-N^{ε}-benzyloxycarbonyl-L-lysine (2.7 g, 7 mmol), DCC (1.47 g, 7 mmol) and N-hydroxybenztriazole (0.96 g, 7.2 mmol) in DMF (15 ml) were stirred together at 0°C and then at room temperature for 30 min.

The dipeptide (**3**) (2.8 g, 5.5 mmol) was treated with anhydrous trifluoroacetic acid at 0° for 30 min. Excess TFA was removed *in vacuo* and the residue triturated with dry ether to give the TFA salt in quantitative yield.

The TFA salt of (**3**) and triethylamine (1.5 ml, 14 mmol) in DMF (10 ml) were added to the above acylating mixture and stirred overnight at room temperature. The tripeptide **4** was isolated from the reaction mixture by aqueous citric acid extraction procedure as earlier in 90% yield; m.p. 86-87°; $[\alpha]_D^{20}$ −29.6 (*c*, 1.0, in DMF); R_f (A) 0.41; R_f (B) 0.69 (Found: C, 55.6; H, 7.0; N, 16.0. $C_{36}H_{52}N_9O_{10}$ requires C, 56.1; H, 6.8; N, 16.3%).

N-Butoxycarbonyl-O-benzyl-L-threonyl-N^{ε}-benzyloxycarbonyl-L-lysyl-L-prolyl-N^{ω}-nitro-L-arginine picolyl ester (**5**)

Compound (**4**) (1 g, 1.3 mmol) was treated with anhydrous trifluoroacetic acid (3 ml) at 0°C for 30 min as usual. The excess acid was removed *in vacuo*, and the residue washed with dry ether, was dried over KOH pellets for 3 hr. The TFA salt and triethylamine (0.48 ml, 3.4 mmol) in DMF (5 ml) was added to a preactivated solution of butoxycarbonyl-O-benzyl-L-threonine (0.525 g, 1.7 mmol), DCC (0.3 g, 1.7 mmol) and N-hydroxybenztriazole (0.25 g, 1.7 mmol) in DMF (8 ml). The mixture was stirred at 0°C for 30 min and then at room temperature for 12-13 hr. The product was isolated by citric acid procedure and recrystallised from dry ether acetate and petrol to give **5** as an analytical pure product (1.1 g) in 82% yield, m.p. 125-27°; $[\alpha]_D^{20}$ −19.5 (*c*, 0.9, in DMF); R_f (A) 0.43; R_f(B) 0.57; R_f (C) 0.63 (Found: C, 58.5; H, 6.7; N, 14.3. $C_{47}H_{65}N_{10}O_{12}$ requires C, 58.7; H, 6.8; N, 14.6%).

N-Benzyloxycarbonyl-L-threonyl-N$^{\varepsilon}$-benzyloxycarbonyl-L-lysyl-L-prolyl-N$^{\omega}$-nitro-L-arginine picolyl ester (**6**)

Compound **4** (3.2 g, 4.2 mmol) was treated with anhydrous trifluoroacetic acid at 0°C for 30 min to give quantitative yield of the TFA salt (**4a**). To a solution of **4a** and triethylamine (1.18 ml, 8.4 mmol) in DMF (20 ml) was added N-benzyloxycarbonyl-L-threonine pentachlorophenyl ester (2.5 g, 5 mmol) and the mixture stirred at room temperature for 13 hr. Isolation by citric acid procedure gave the protected tetrapeptide (**6**) in 84.5% yield as a colourless powder; R_f (A) 0.24; R_f (C) 0.34; $[\alpha]_D^{20} -20.2$ (*c*, 0.9, in DMF) (Found: C, 56.9; H, 6.6; N, 15.3. $C_{43}H_{57}N_{10}O_{12}$ requires C, 57.0; H, 6.3; N, 15.5%).

L-Threonyl-L-lysyl-L-prolyl-L-arginine-triacetate (tuftsin) (**7**)

The protected tetrapeptide (**5**) (3 g, 5.1 mmol), dissolved in methanol and acetic acid (1 : 1, 10 ml) was hydrogenated for 12 hr over Pd/C (10%, 500 mg). The catalyst was foltered off through celite and washed well with acetic acid (50 ml). The washings and filtrate were combined, and evaporated to give a colourless gum which was dissolved in acetic acid (50%, 1 ml) and chromatographed on a column of Bio-gel P-2 (200-400 mesh, 2.5 × 90 cm), equilibrated in the same solvent. The fractions containing the peptide (Sakaguchi reagent positive) were combined and evaporated, taken up again in water (3 ml), millipore filtered and freeze-dried to give tuftsin triacetate as fluffy, colourless solid (0.9 g, 53%); $[\alpha]_D^{20} -60.2$; (*c*, 1, in AcOH); R_f (D) 0.38 (Found: C, 47.5; H, 8.0; N, 16.6; $C_{21}H_{40}N_8O_6.3CH_3COOH$ requires C, 47.6; H, 7.6; N, 16.5%).

Similarly protected tetrapeptide (**6**) (2.5 g, 2.56 mmol) dissolved in methanol and acetic acid (1 : 1, 7 ml) was hydrogenated for 16 hrs using palladium charcoal (10%, 600 mgs) as catalyst. The catalyst was filtered through celite and washed well with aqueous acetic acid (50%). Combined filtrate was evaporated *in vacuo*. The residue was then treated with TFA for 30 min, and precipitated with dry ether. The solid so obtained was dissolved in water (0.5 ml) and purified by the procedure mentioned above and converted to acetate salt using ion-exchange resin IRA-45. The tuftsin triacetate was obtained after freeze-drying the eluate as a white fluffy solid (0.75 g, 55%).

Biological testing

For biological verification of the tetrapeptide, augmentation of phagocytosis by polymorphonuclear leukocytes, was observed with the synthetic product. Normal human leukocytes were separated by dextran density gradient method and incubated with *Canadida albicans*, the amount of phagocytosis was observed by the reduction[18,19] of nitro blue tetrazolium in Shimadzu spectrophotometer. Synthetic peptide showed full bioactivity of natural tuftsin.

Acknowkedgement

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Antiparasitic Agents: Part 5—Synthesis of 4-(Substituted-aryl)amino-7-chloroquinolines as Potential Antimalarial Agents‡

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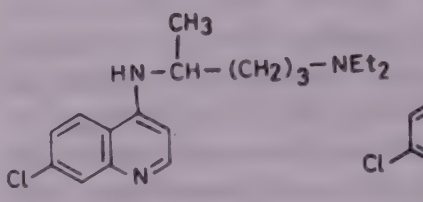
A series of 4-(4- and 3-substituted-aryl)amino-7-chloroquinolines (**11-15**, **17**,**18**,**28**) and substituted diphenyl sulphones (**8-10**, **19-27**) have been synthesized and tested for their antiparasitic activity against *Plasmodium berghei* in mice, *Litomosoides carinii* in cotton rats and *Hymenolepis nana* in mice. Of the compounds tested, **11** shows 100% activity against *P. berghei* at a dose of 10 mg/kg × 5 days in mice while **23** is effective in eliminating 100% of the *H. nana* worms from mice at a single oral dose of 250 mg/kg.

Amongst the pharmacophores that have been incorporated into potential antiparasitic agents, 4-amino-7-chloroquinoline and diphenyl sulphone have proved to be highly effective and have led to the discovery of clinically important antimalarials **1-4** and DDS (**5**) respectively[1,2]. In continuation of our earlier efforts[3-6] on the development of new effective antiparasitic agents, we have presently synthesized some 7-chloro-4-substituted-quinolines (**11-28**) which may provide synergistic combination of 4-amino-quinoline and DDS with better chemotherapeutic effects. This approach seems to have drawn lesser attention in the SAR studies of this class of compounds.



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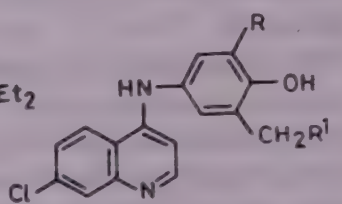
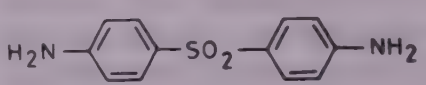


2 R = H, R^1 = NEt_2
3 R = H, R^1 = N
4 R = CH_2NEt_2, R^1 = NEt_2



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Condensation of 4-chloronitrobenzene and 4-chloroacetanilide in the presence of sodium sulphide led to 4-nitro-4′-acetamidodiphenyl sulphone (**6**)[7] (Scheme 1). Potassium permanganate oxidation of **6** resulted in **8** which on deacetylation with dil HCl yielded **9**[7]. Catalytic hydrogenation (Raney-nickel) of **9** gave **10**, which on condensation with 4,7-dichloroquinoline gave (**11**). Reduction of **11** with Raney-nickel and hydrazine hydrate smoothly led to the formation of **12**. Treatment of **12** with thiophosgene gave 7-chloro-4-(4-isothiocyanato-diphenylsulphon-4-yl)aminoquinoline (**13**). Reaction of **12** with ethyl isothiocyanate and ethyl chloroformate yielded **14** and **15** respectively. Compound (**14**) was also obtained by the condensation of **13** with ethyl amine (Scheme 1).

Catalytic hydrogenation (Raney-nickel) of **7** led to 4,4′-diaminodiphenyl sulphide (**16**) which on condensation with 4,7-dichloroquinoline gave 4,4′-bis(7-chloroquinoline-4-yl) aminodiphenyl sulphide (**17**). $KMnO_4$ oxidation of **17** failed to give the desired sulphone (**18**) apparently due to its poor solubility. Compound (**18**), however, was prepared by the condensation of 4,7-dichloroquinoline with **10** (Scheme 1).

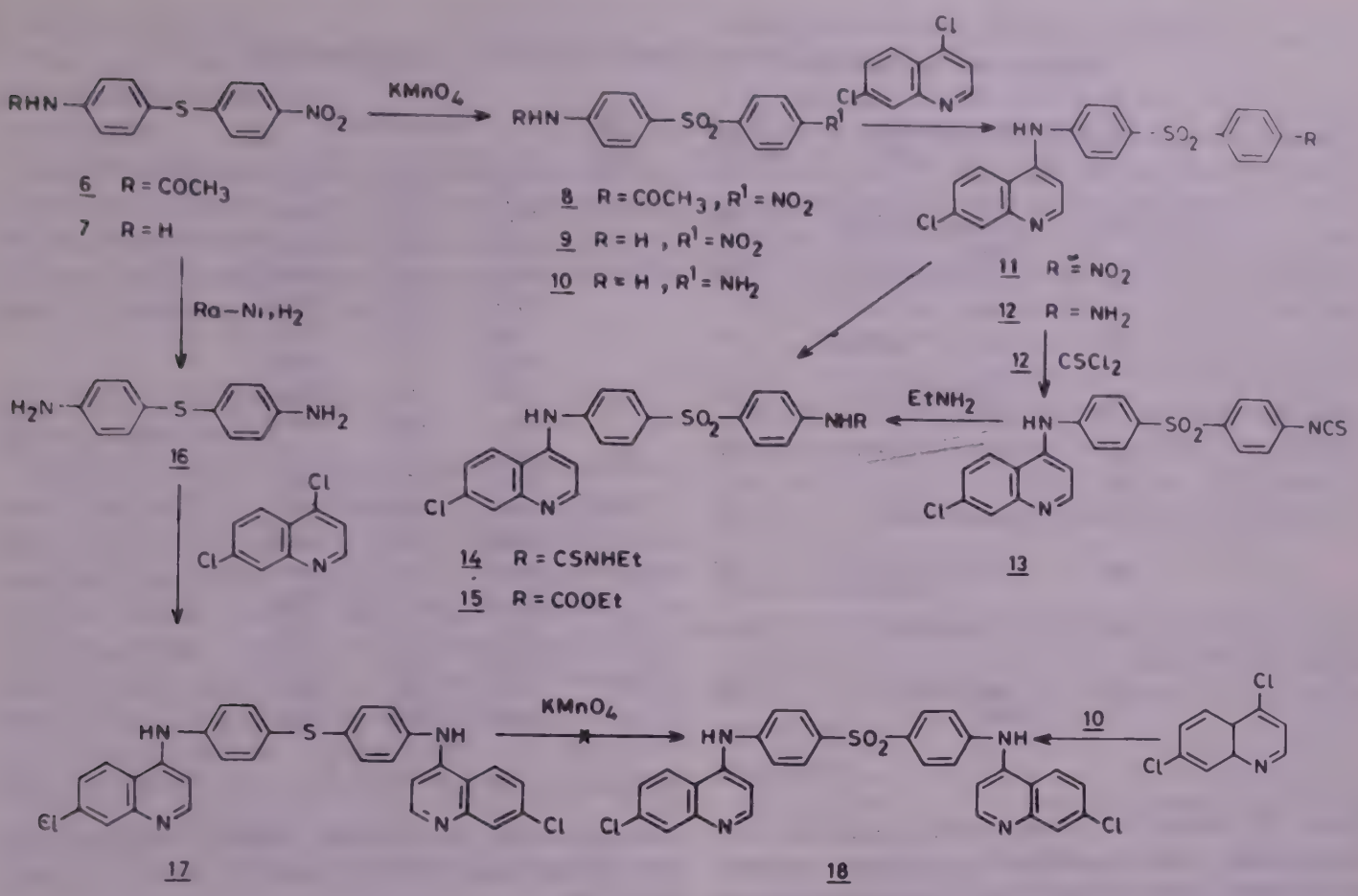
The 4,4′-diacetamidodiphenyl sulphone (**20**) obtained by the acetylation of **10**, was brominated to yield the dibromo compound (**21**). Deacetylation of **21** followed by reaction of thiophosgene on resulting amine (**22**) led to the formation of 3,3′-dibromo-4,4′-diisothiocyanadodiphenyl sulphone (**23**). Condensation of **23** with N-methylpiperazine and N-benzylpiperazine yielded the corresponding thioureas (**24**) and (**25**) (Scheme 2).

Nitration of 4,4′-difluorodiphenyl sulphide (**19**) led to the corresponding 3,3′-dinitro derivative (**26**)[8] which on reduction with Raney-nickel/hydrazine hydrate gave the 3,3′-diamino derivative (**27**). Condensation of **27** with 4,7-dichloroquinoline gave 3,3′-bis(7-chloroquinolin-4-yl)amino-4,4′-difluorodiphenyl sulphone (**28**) (Scheme 2).

Biological activity

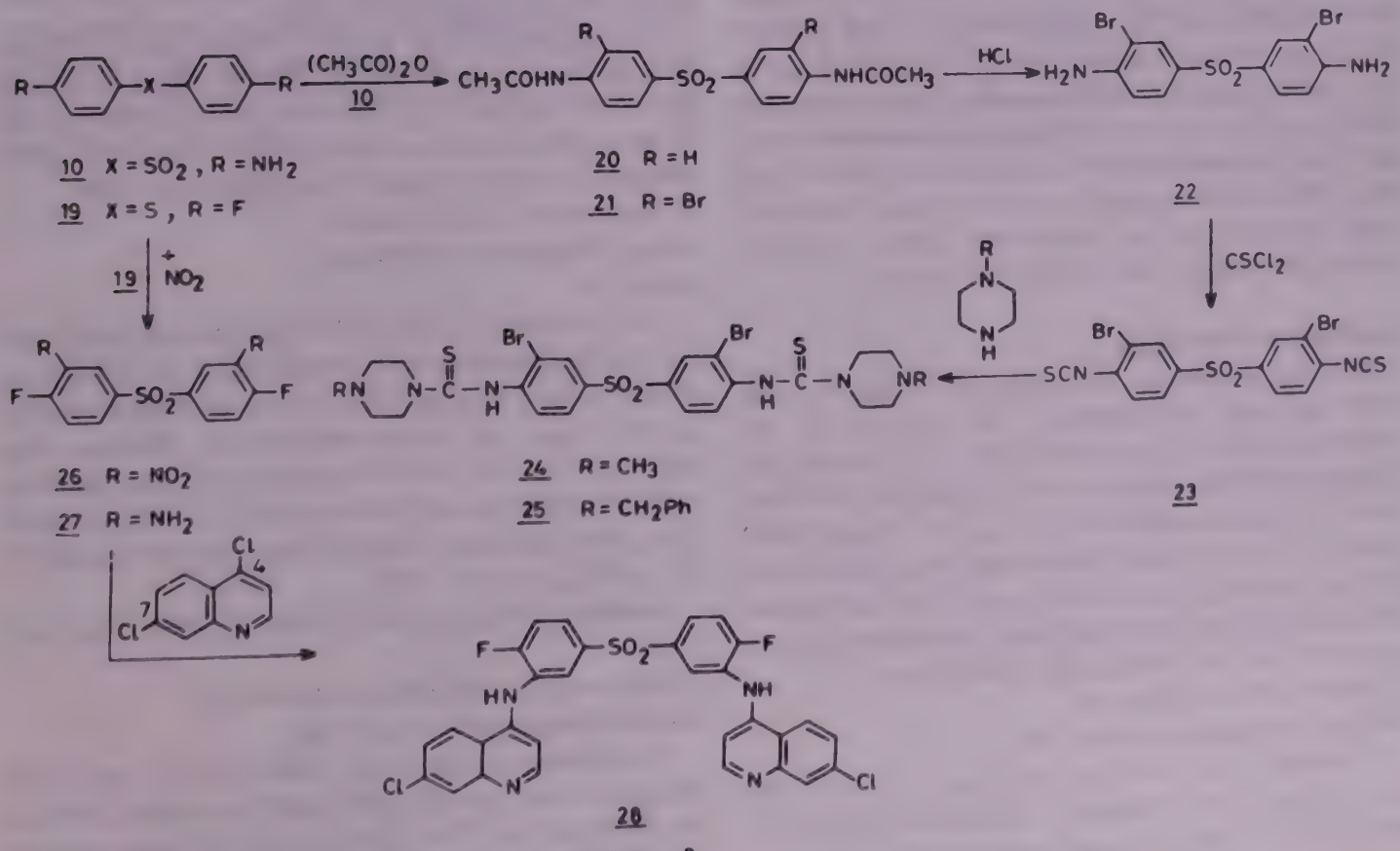
All the 7-chloro-4-(substituted)aminoquinolines

†For Parts 1-4 of this series see references 3-6.
‡Communication No. 3879 from CDRI, Lucknow.



6 R = $COCH_3$
7 R = H
8 R = $COCH_3$, R^1 = NO_2
9 R = H, R^1 = NO_2
10 R = H, R^1 = NH_2
11 R = NO_2
12 R = NH_2
13
14 R = CSNHEt
15 R = COOEt
16
17
18

Scheme – 1



Scheme – 2

Table 1—Characterisation Data of Compounds (**11-15**, **17**, **18**, **23** and **28**)

Compd	Mol. formula (M^+)	m.p. (°C)	Yield (%)	Found (Calc) % (C)	(H)	(N)
11	$C_{21}H_{14}Cl_2N_3O_4S$ (439)	280	79	57.1 (57.4)	3.4 (3.1)	9.8 (9.5)
12	$C_{21}H_{16}ClN_3O_2S$ (409)	250	80	61.9 (61.6)	4.2 (3.9)	10.0 (10.3)
13	$C_{22}H_{14}ClN_3O_2S_2$	250	63	58.9 (58.5)	2.9 (3.1)	9.0 (9.3)
14	$C_{24}H_{21}ClN_4O_2S_2$	155	66	58.4 (58.1)	4.5 (4.2)	11.1 (11.3)
15	$C_{24}H_{20}ClN_3O_4S$	195	62	60.2 (59.9)	3.8 (4.2)	8.4 (8.7)
17	$C_{30}H_{20}Cl_2N_4S$	250	78	67.2 (66.9)	3.5 (3.7)	10.1 (10.4)
18	$C_{30}H_{20}Cl_2N_4O_2S$	280	68	66.8 (66.9)	3.3 (3.7)	9.9 (10.4)
23	$C_{14}H_6Br_2O_2S_3$	230-32	70	34.5 (34.3)	1.5 (1.2)	5.4 (5.7)
28	$C_{30}H_{18}Cl_2F_2N_4$ (606)	280	55	59.7 (59.4)	3.2 (3.0)	8.8 (9.2)

(**11-15**, **17**, **18** and **28**) (Table 1) were tested for their antimalarial and antifilarial activities against *Plasmodium berghei* in mice[9] and *Litomosoides carinii* in cotton rats[10] respectively. The symmetrical sulphides and sulphones were evaluated for their antitapeworm activity against *Hymenolepis nana* in mice[10].

Amongst the compounds (**11-28**) tested, **11** exhibited 100% reduction of the parasitaemia in mice infected with *P. berghei* at an intraperitoneal dose of 10 mg/kg × 5 days. Compound (**11**) was also found to possess slow microfilaricidal action against *L. carinii* in cotton rats at an intraperitoneal dose of 30 mg/kg given for 5 days. When tested against *H. nana* in mice, **23** showed 100% clearance of the tapeworms along with their scolices at a single oral dose of 250 mg/kg.

Experimental Procedure

Melting points were determined on a sulphuric acid bath and are uncorrected. The purity of the compounds was routinely checked by TLC on silica gel G plates. IR(KBr) spectra were recorded on a Perkin-Elmer 157 spectrophotometer (ν_{max} cm^{-1}) and PMR spectra in TFA solution, unless otherwise stated, on a Perkin-Elmer R-32 instrument using TMS as internal standard (chemical shifts in δ ppm). Mass spectra were recorded on a Jeol JMSD-300 spectrometer.

7-Chloro-4-(4′-nitrodiphenyl-sulphon-4-yl)aminoquinoline (**11**)

A solution of 4,7-dichloroquinoline (1.9 g, 0.01 mol) and 4-amino-4′-nitrodiphenyl sulphone (**9**) (2 g, 0.01 mol) in EtOH (200 ml) was refluxed for 24 hr. The solid thus separated was filtered, washed with H_2O and crystallised from EtOH to give **11**, yield 3.5 g (79%) m.p. 250°.

Compounds **17**,**18**,**28** were prepared similarly by treating 4,7-dichloroquinoline (2 mol) with **16**,**10** and **27** respectively.

7-Chloro-4-(4′-aminodiphenyl-sulphon-4-yl)aminoquinoline (**12**)

A solution of **11** (4.3 g, 0.001 mol) in EtOH (100 ml) was refluxed in presence of Raney nickel (1 g) and hydrazine hydrate (2 g, 0.04 mol) for 1 hr, filtered, the filtrate concentrated and the residue crystallized from ethanol to give **12**, yield 3.3 g (80%), m.p. 250°.

7-Chloro-4-(4′-isothiocyanato-diphenylsulphon-4-yl)aminoquinoline (**13**)

Thiophosgene (0.4 ml, 0.005 mol) in acetone (15 ml) was added dropwise to a stirred solution of **12** (1 g, 0.0025 mol) in acetone (150 ml) and triethylamine (0.8 g, 0.01 mol) at room temperature. Stirring was continued for 8 hr, solvent removed *in vacuo* and the solid obtained, washed with water (3 × 10 ml), hexane (3 × 10 ml) and recrystallized from acetone to yield **13** (0.7 g 63%), m.p. > 250°.

Similarly **23** was prepared from **22**; yield 70%, m.p. 232-34°.

7-Chloro-4-[(4-N-ethylthiocarbamoryl)-aminodiphenylsulphon-4-yl] (**14**)

A solution of **12** (1 g, 0.0025 mol) and ethyl isothiocyanate (0.43 g, 0.005 mol) in acetone (100 ml) was refluxed for 10 hr. The solvent was removed and the residue crystallised from EtOH to give **14**, yield 0.8

g, (66%), m.p. 155°.

7-Chloro-4-[(4-carboethoxy)amino-diphenylsulphon-4-yl]amino-quinoline (**15**)

Ethyl chloroformate (2.16 g, 0.02 mol) was added to a solution of **13** (4.09 g, 0.01 mol) in pyridine (60 ml) and the reaction mixture kept at 70° for 2 hr. Removal of solvent and crystallisation of the residue from EtOH gave **15**, yield 3.0 g (62%), m.p. 195°.

3,3'-Dibromo-4,4'-diacetamino-diphenyl sulphone (**21**)

Bromine (1.6 g, 0.02 mol) was added dropwise to a stirred solution of 4,4'-acetaminodiphenyl sulphone (**20**, 3.2 g, 0.01 mol) in acetic acid (15 ml). Stirring was continued for further 4 hr at room temperature, the reaction mixture poured onto crushed ice, and the solid filtered and crystallized from acetic acid-water to give **21**, yield 3.5 g (73%) m.p. 258-60°; IR: 1700 (CO); PMR: 2.0 (*s*, 6H, CO−CH_3), 7.75 (*m*, 4H, Ar−H, 2.2', 3,3'), 10.1 (*s*, 2H, Ar−H 6,6'); MS: *m/z*: 490 (M^+) (Found: C, 39.5; H, 3.2; N 5.5. $C_{16}H_{24}N_2O_4S$ requires C, 39.2; H, 2.9, N, 5.7%).

3,3'-Dibromo-4,4'-diaminodiphenyl-sulphone (**22**)

Compound (**21**, 3.989 g, 0.01 mol) in dil HCl (50 ml) was refluxed for 6 hr. The reaction mixture was neutralized with liquor ammonia. Solid thus obtained was filtered and crystallized from ethanol to afford **22**, yield 2.5 g (81%), m.p. 160°; IR: 3200-3400 (NH_2) (Found: C, 47.3; H, 2.9; N, 8.9. $C_{12}H_8Br_2N_2O_4S$, C, 47.1; H, 2.6; N, 9.2%).

4,4'-Di-(4-N-methylpiperazino-thiocarbonyl)amino-3,3'-di- bromodiphenyl sulphone (**24**)

A solution of **23** (4.9 g, 0.001 mol) and N-methylpiprazine (3.33 g, 0.02 mol) in dry acetone (50 ml) was stirred for 8 hr. The solvent was removed *in vacuo* and the solid obtained crystallized from acetone to furnish **24**, yield 0.3 g (43%), m.p. 236°; IR: 3300-3400 (NH), 2900 (CH); PMR (TFA): 3.0 (*s*, 6H, N−CH_3); 3.2-4.6 (*m*, 6H, N-(CH_2)$_4$) 7.3-10.1 (*m*, 6H, Ar−H) (Found: C, 41.4; H, 4.7; N, 13.6. $C_{24}H_{30}Br_2N_6S_3O_2$ requires C, 41.7; H, 4.3; N, 13.9%).

Similarly **25** was prepared from **23**, m.p. 242°; IR: 3300-3400 (NH), 2900 (CH); PMR (TFA): 3.1-4.8 [(*m*, 20H, N-(CH_2)$_{10}$] 7.1-10.0 (*m*, 12H, Ar−H) (Found: C, 51.4; H, 4.8; N, 11.1. $C_{36}H_{38}Br_2N_6O_2S_3$ requires C, 51.3; H, 4.5, N, 11.4%).

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Synthesis of 2,5(6)-Disubstituted-benzimidazoles, 2-Substituted-5-(4-substituted-phenyl)-1,3,4-thiadiazoles & Imidazothioxanthene & Their Antifilarial Activity†

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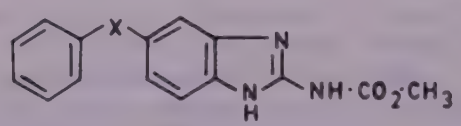
2-Carbomethoxyaminothioxantheno[2,3-*d*]imidazol-12-one-13,13-dioxide (**5**), 2,5(6)-disubstituted-benzimidazoles (**10-13**) and 2-substituted-5-(3-nitro-4-substituted-phenyl)-1,3,4-thiadiazoles (**18-24**) have been synthesized and evaluated for their antifilarial activity. No promising activity is shown by these compounds.

The efficacy of substituted benzimidazoles[1-3] as mebendazole (**a**), febendazole (**b**) and thiadiazoles[4-5] in the treatment of parasitic infections is well known.

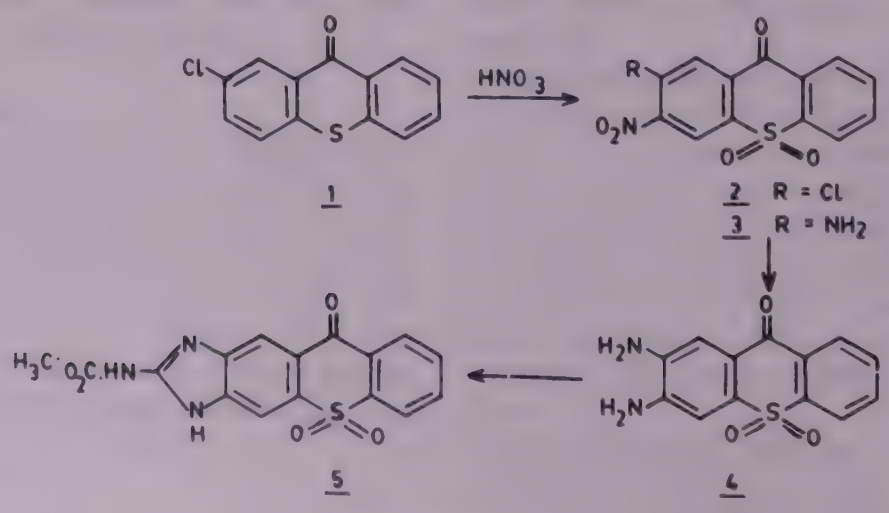


a ; X = CO
b ; X = S

Several arylisothiocyanates[6] have been shown to possess high nematodicidal activity in man. Benzimidazole and thiadiazole moieties substituted especially with isothiocyanate and piperazines[7-8] are established pharmacophores in parasitic chemotherapy. We have incorporated these pharmacophores in some of the compounds designed as potential antifilarial agents. In the present paper, we report the synthesis and antifilarial activity of 2-carbomethoxyamino thioxantheno[2,3-*d*]imidazol-12-one-13,13-dioxide (**5**), 2,5(6)-disubstituted-benzimidazoles (**10-13**) and 2-substituted 5-(3-nitro-4-substituted-phenyl)-1,3,4-thiadiazoles (**18-24**).

Nitration of 2-chlorothioxanthone (**1**) gave 2-chloro-3-nitrothioxanth-9-one-10,10-dioxide (**2**) which on treatment with ammonia in dimethylformamide yielded 2-amino-3-nitrothioxanth-9-one-10,10-dioxide (**3**). Reduction of **3** with Raney nickel and hydrazine hydrate gave 2,3-diaminothioxanth-9-one-10,10-dioxide (**4**) which on cyclisation with 1,3-dicarbomethoxy-S-methylisothiourea in refluxing ethanol afforded the 2-carbomethoxyaminoimidazothioxantheno[2,3-*d*]imidazol-12-one-13,13-dioxide (**5**) (Scheme 1).

Treatment of terephthalic acid with phosphoryl chloride produced the corresponding diacid chloride

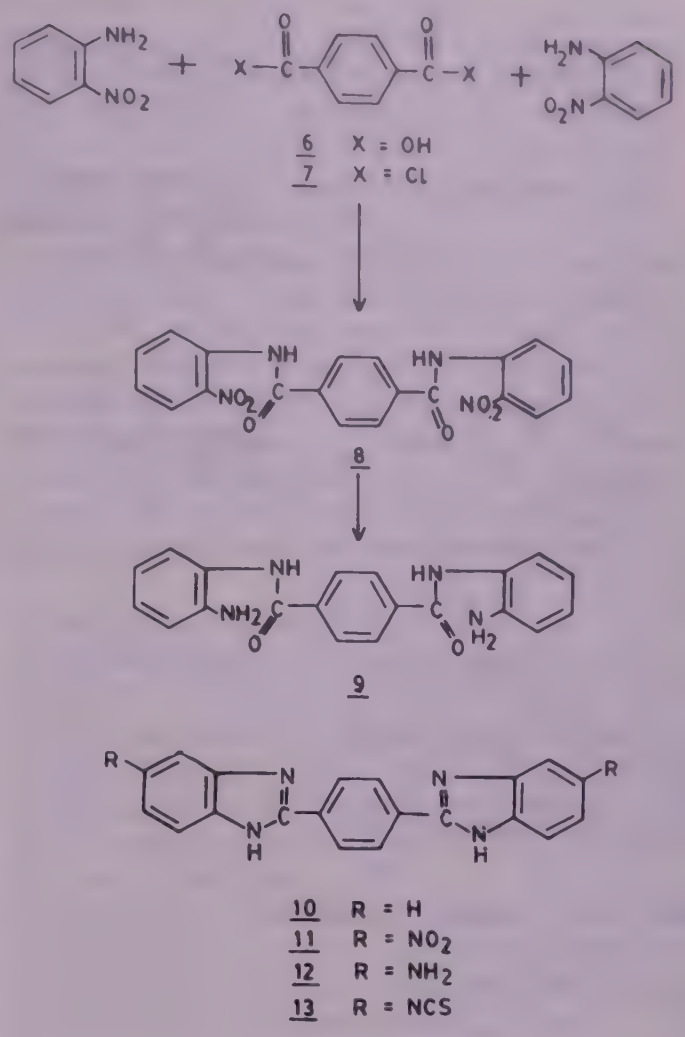


Scheme 1

†CDRI Communication No. 3772

(7) which was condensed with *o*-nitroaniline to give **8**. Reduction of **8** with Raney nickel followed by cyclisation with dil. hydrochloric acid yielded 1,4-bis(2-benzimidazolyl)benzene[9] (**10**). Nitration of **10** gave 1,4-bis(5-nitro-2-benzimidazolyl)benzene (**11**). Reduction of **11** with zinc-acetic acid yielded 1,4-bis(5-amino-2-benzimidazolyl)benzene (**12**). Treatment of **12** with thiophosgene afforded 1,4-bis(5-isothiocyanato-2-benzimidazolyl)benzene (**13**) (Scheme 2).

Treatment of 4-chlorobenzoic acid (**14**) with thionyl chloride gave the corresponding acid chloride (**15**) which was condensed with thiosemicarbazide to give the aroylthiosemicarbazide (**16**). Cyclisation of **16** with phosphoric acid yielded 2-amino-5-(4-chlorophenyl)-1,3,4-thiadiazole[10] (**17**). Nitration of **17** gave 2-amino-5(4-chloro-3-nitrophenyl)-1,3,4-thiadiazole (**18**; Table 1). Mechanistically three, five and three are the only the sites of electrophilic substitution in the cases of nitration of **1**, **10** and **17**. Condensation of **18** separately with piperazine, N-phenylpiperazine, N-benzylpiperazine and 2-aminobenzimidazole in pyridine gave the corresponding 2-amino-5-(3-nitro-4-substituted-phenyl)-1,3,4-thiadiazoles (**19-21** and **24**) and treatment of **19** with benzoyl chloride and ethyl chloroformate in pyridine gave **22** and **23** respectively (Scheme 3) (Table 1).



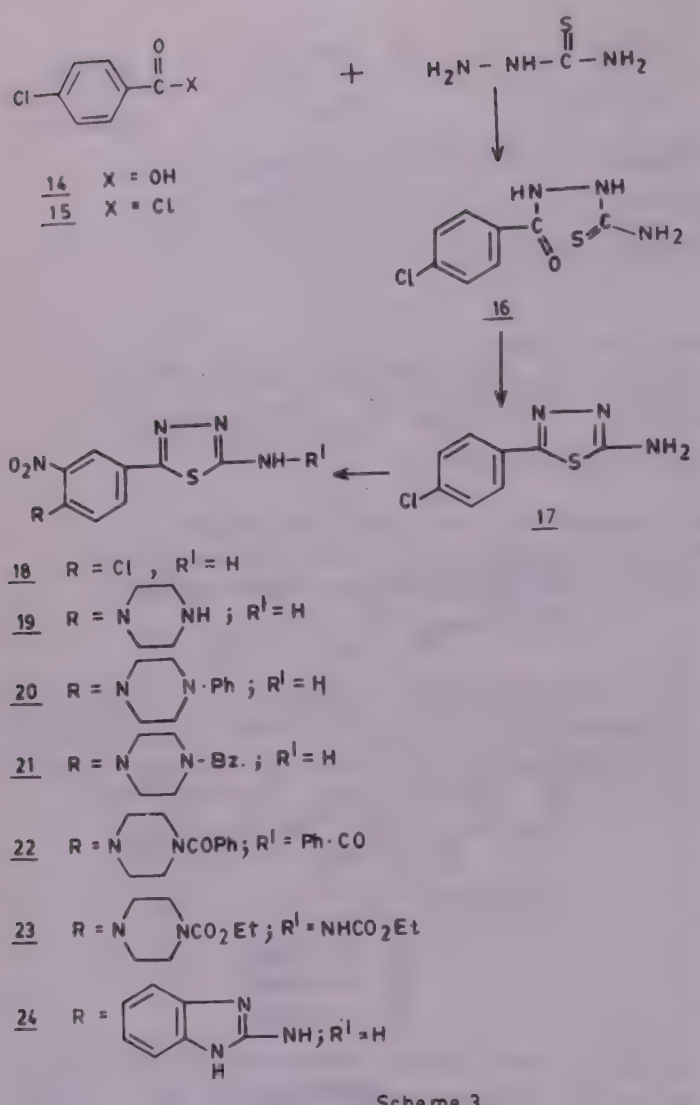
Scheme 2

Biological activity

The compounds **2-5**, **10-13** and **18-24** were evaluated both for micro- and macro-filaricidal activities against

Table 1—Characterisation Data of 2-Substituted 5-(3-nitro-4-substituted-phenyl)-1,3,4-thiadiazoles (**19-24**)

Compd	m.p. °C	Yield (%)	Mol. formula (M^+)	Analysis	Found	Calcd	PMR (TFA) δ, ppm
19	>250	50	$C_{12}H_{14}N_6O_2S$	C:	47.5	47.1	3.55 [*m*, 5H, H−N (CH_2)$_2$]
				H:	4.9	4.6	3.85 [*m*, 4H, N (CH_2)$_2$],
				N:	27.1	27.5	7.1-8.6 (*m*, 3H, Ar−*H*)
20	>280	52	$C_{18}H_{18}N_6O_2S$	C:	56.2	56.5	3.5-4.1 [*m*, 8H, −N (CH_2)$_2$
				H:	5.1	4.7	and Ph−N (CH_2)],
				N:	21.5	21.9	7.1-8.8 (*m*, 8H, Ar−*H*),
21	>280	60	$C_{19}H_{20}N_6O_2S$	C:	58.0	57.5	3.35 [*m*, 4H, −N (CH_2)$_2$],
			(396)	H:	5.1	4.8	3.7 [*m*, 4H, Ph−CH_2−N(CH_2)$_2$],
				N:	20.8	21.2	4.25 (*s*, 2H, Ph−CH_2),
							7.1-8.5 (*m*, 8H, Ar−*H*)
22	>280	70	$C_{26}H_{22}N_6O_4S$	C:	61.1	60.7	—
				H:	4.7	4.3	
				N:	16.0	16.3	
23	>280	65	$C_{18}H_{22}N_6O_6S$	C:	48.4	48.0	1.1-1.4 (*m*, 6H, 2×CH_2−CH_3),
			(450)	H:	5.2	4.9	3.5 (*m*, 4H, 2×CH_2−CH_3),
				N:	18.3	18.7	3.8-4.2 (*m*, 8H, N(CH_2)$_2$ and
							−CO−N (CH_2)$_2$],
							7.1-8.8 (*m*, 3H, Ar−*H*)
24	>250	60	$C_{15}H_{11}N_7O_2S$	C:	51.3	51.0	—
				H:	3.5	3.1	
				N:	27.4	27.8	



Scheme 3

Litomosoides carinii in cotton rats by the method of Hawking and Swell[11,12] and were found to be inactive at a dose of 30 mg/kg × 5 days.

Experimental Procedure

Melting points were determined in a sulphuric acid-bath and are uncorrected. Homogeneity of the compounds was routinely checked on silica gel G TLC plates. IR(KBr) spectra were recorded on a Perkin-Elmer 157 spectrometer (ν_{max} in cm^{-1}) and PMR spectra in TFA solution, unless otherwise stated, on a Perkin-Elmer R-32 instrument using TMS as internal standard (chemical shift in δ, ppm). Mass spectra were recorded on a Jeol JMS D-300 spectrometer.

2-Chloro-3-nitrothioxanth-9-one- 10,10-*dioxide* (**2**)

A mixture of 2-chlorothioxanthone **1** (2.46 g, 0.01 mol) H_2SO_4 (25 ml, d = 1.84) and nitric acid (1 ml, d = 1.42) at 0° was stirred for 1/2 hr and poured on crushed ice. The solid thus separated was filtered, washed with water, dried and crystallized from ethanol to give **2** (2.5 g, yield 77%), m.p. 165°, IR: 1680 (CO), 1550, 1305 (NO_2); MS: *m/z* 323 (M^+) (Found: C, 48.5; H, 2.1; N, 4.7. $C_{13}H_6ClNO_5S$ requires C, 48.3; H, 1.9; N, 4.3%).

2-Amino-3-nitrothioxanth-9-one- 10,10-*dioxide* (**3**)

Ammonia gas was passed into a solution of **2** (3.2 g, 0.01 mol) in DMF (40 ml) at 150° for 8 hr. The resulting mixture was cooled and diluted with water. The product thus obtained was filtered and crystallised from EtOH to afford **3** (1.5 g, yield 50%), m.p. 195°; IR: 3200-3400 (NH_2), 1675 (CO), 1150 (SO_2); MS: *m/z* 304 (M^+) (Found: C, 51.4; H, 3.0; N, 8.9. $C_{13}H_8N_2O_5S$ requires C, 51.1; H, 2.6; N, 9.2%).

2,3-*Diaminothioxanth-9-one-* 10,10-*dioxide* (**4**)

To a mixture of **3** (6.0 g, 0.02 mol) and Raney-nickel (~1 g) in EtOH (50 ml) at 75° a solution of hydrazine hydrate (16 g, 0.16 mol) in EtOH (20 ml) was added dropwise and the mixture refluxed for 1 hr. The catalyst was filtered off and the solvent from the filtrate removed. The product so obtained was crystallised from EtOH to give **4** (3.29 g, yield 59%), m.p. 150°; IR: 3200-3400 (NH_2), 1670 (CO), 1150 (SO_2).

2-Carbomethoxyaminothioxantheno-
[2,3-*d*]*imidazol-12-one-*13,13-*dioxide* (**5**)

A solution of **4** (2.7 g, 0.01 mol) and 1,3-dicarbethoxy-S-methylisothiourea (2.52 g, 0.12 mol) in EtOH (100 ml) was refluxed for 12 hr. The resulting mixture was cooled. The solid thus obtained was filtered and crystallization from AcOH – H_2O to give **5** (2.1 g, yield 81%), m.p. 220°; IR: 1700 (CO_2Me), 1680 (CO); PMR: 3.9 (*s*, 3H, CO_2CH_3), 7.5-8.5 (*m*, 6H, Ar – *H*) (Found: C, 54.1; H, 3.4; N, 11.4. $C_{16}H_{11}N_3O_5S$ requires C, 53.8; H, 3.1; N, 11.8%).

N,N'-Di-(o-nitrophenyl)terephthalamide (**8**)

A solution of the acid chloride **7** (2.02 g, 0.01 mol) in dry C_6H_6 (25 ml) was added dropwise to a stirred solution of 2-nitroaniline (2.76 g, 0.01 mol) in dry C_6H_6 and TEA (2.0 g, 0.02 mol) at ambient temperature. The stirring was continued for 14 hr. The solid thus separated was filtered, washed with H_2O (2 × 10 ml) and crystallised from EtOH to give **8**, yield 3 g (75%), m.p. 190°; IR: 3400 (NH), 1670 (CO), 1510, 1340 (NO_2); MS: *m/z* 406 (M^+) (Found: C, 59.5; H, 3.7; N, 13.3. $C_{20}H_{14}N_4O_6$ requires C, 59.1; H, 3.4; N, 13.8%).

N,N'-Di-(o-aminophenyl)terephthalamide (**9**)

A suspension of **8** (4.0 g, 0.01 mol) in EtOH (200 ml) and Raney-nickel (1.0 g) was shaken on a paar-hydrogenerator at 3.5 kg/cm² pressure for 8 hr. The catalyst was filtered off and washed with hot EtOH (3 × 20 ml). The solvent was removed from the filtrate and the product crystallised from EtOH to give **9** (2.5 g, yield 72%), m.p. 150°; IR: 3200-3400 (NH_2), 1640 (CO).

1,4-*Bis*(2-*benzimidazolyl*)*benzene* (**10**)

A solution of **9** (3.46 g, 0.01 mol) in EtOH (30 ml) and conc. HCl (20 ml) was refluxed for 10 hr. The resulting mixture was cooled, the solid that separated was filtered, suspended in H_2O basified with aq. NH_4OH solution, filtered and crystallised from DMF – H_2O (1.8 g, yield 58%), m.p. 250°; IR: 3200 (NH), 1630 (C=N); MS: *m/z* 310 (M^+) (Found: C, 77.7; H, 4.5; N, 17.8. $C_{20}H_{14}N_4$ requires C, 77.4; H, 4.5; N, 18.1%).

1,4-*Bis*(5-*nitrobenzimidazolyl*)*benzene* (**11**)

To an ice cooled (0°) solution of **10** (3.10 g, 0.01 mol) in conc. H_2SO_4 (10 ml) was added dropwise fuming HNO_3 (1 ml, d = 1.5) during 20-30 min with stirring. The stirring was continued for 1 hr and the resulting mixture poured onto crushed ice. The solid that separated out was filtered, washed with H_2O (3 × 30 ml), dried and crystallised from DMF-H_2O to give **11**, yield 3 g (75%), m.p. > 300°; IR: 3200-3300 (NH), 1640 (C=N), 1530, 1320 (NO_2) (Found: C, 60.5; H, 3.3; N, 19.7. $C_{20}H_{12}N_6O_4$ requires C, 60.0; H, 3.0; N, 21.0%).

1,4-*Bis*(5-*amino*-2-*benzimidazolyl*)-*benzene* (**12**)

Zinc dust (3.6 g, 0.06 atom) was added to a stirred solution of **11** (4.0 g, 0.01 mol) in AcOH (50 ml) at 0°. The stirring was continued for 3 hr and then filtered. The solvent was removed from the filtrate *in vacuo*, and the residue washed with liquor NH_4OH (10 ml) and crystallized from acetic acid-H_2O to give **12** (2.5 g, yield 73%), m.p. 250°; IR: 3200-3400 (NH_2), 1640 (C=N) (Found: C, 70.1; H, 5.1; N, 24.5. $C_{20}H_{16}N_6$ requires C, 70.6; H, 4.7; N, 24.7%).

1,4-*Bis*(5-*Isothiocyanato*-2-*benzimid-azolyl*)*benzene* (**13**)

Thiophosgene (2 ml, 0.26 mol) in acetone (50 ml) was added dropwise to a stirred solution of **12** (3.4 g, 0.01 mol) and $(Et)_3N$ (2.05, 0.02 mol) in acetone (100 ml) at ambient temperature. The stirring was continued for 12 hr. The excess of reagent and the solvent were removed *in vacuo*. The solid thus obtained was washed with H_2O (3 × 30 ml) and crystallised from acetone to give **13** (3 g, yield 7%), m.p. 300°; IR: 3200-3400 (NH), 2100 (NCS), 1615 (C=N) (Found: C, 62.5; H, 3.1; N, 19.5. $C_{22}H_{12}N_6S_2$ requires C, 62.3; H, 2.8; N, 19.8%).

2-*Amino*-5-(4-*chloro*-3-*nitrophenyl*)-1,3,4-*thiadiazole* (**18**)

Nitric acid was added dropwise to an ice cooled solution of **17** (2.0 g, 0.01 mol) in conc. H_2SO_4 (15 ml) added during 10 min with stirring. The stirring was continued for 1 hr and the resulting mixture poured onto crushed ice. The separated solid was filtered, washed with H_2O (3 × 10 ml) and NH_4OH solution (15 ml) and crystallised from DMF – H_2O (2 g, yield 80%), m.p. > 250°; IR: 3100-3300 (NH_2), 1540, 1340 (NO_2), MS: *m/z* 256 (M^+) (Found: C, 37.9; H, 2.3; N, 21.6. $C_8H_5ClN_4O_2S$ requires C, 37.5; H, 2.0; N, 21.7%).

2-*Amino*-5-[3-*nitro*-4-(4-*phenyl*-1-*piperazinyl*)-*phenyl*]-1,3,4-*thiadiazole* (**19**)

A solution of anhyd. piperazine (1.4 g, 0.15 mol) and **18** (2.56 g, 0.01 mol) in pyridine (50 ml) was refluxed for 10 hr. The solvent was removed *in vacuo* and the resultant solid was washed with H_2O (3 × 50 ml) and crystallized from DMF – H_2O to give **19**, (2.0 g, yield 50%), m.p. > 250°.

Similarly, **20**, **21** and **24** (Table 1) were prepared by reacting **18** separately with N-phenylpiperazine, N-benzylpiperazine and 2-aminobenzimidazole.

2-*Benzoylamino*-5-[3-*nitro*-4-(4-*benzoyl*-1-*piperazinyl*)*phenyl*]-1,3,4-*thiadiazole* (**22**)

Benzoyl chloride (3.7 g, 0.03 mol) was added dropwise to a stirred solution of **19** (3.0 g, 0.01 mol) in pyridine (5 ml) and C_6H_6 (50 ml). The stirring was continued for 8 hr. The solvent was removed *in vacuo* and the residue crystallized from DMF – H_2O to give **22**, yield 3 g (64%), m.p. > 250°.

Similarly, 2-carbomethoxyamino-5-[3-nitro-4(4-carboethoxyamino-1-piperazinyl)phenyl]-1,3,4-thiadiazole (**23**) was prepared by reacting ethyl chloroformate with **19**.

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Synthesis of New Analogues of Furapiole, a Potent Insecticide Synergist†

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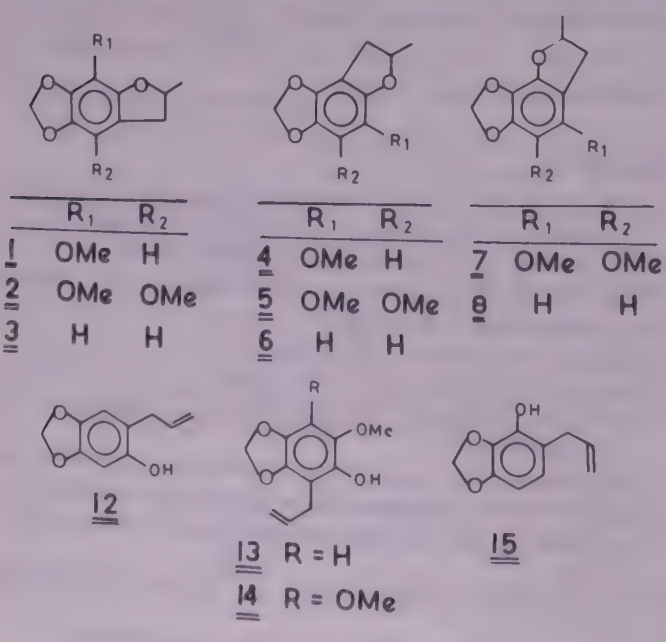
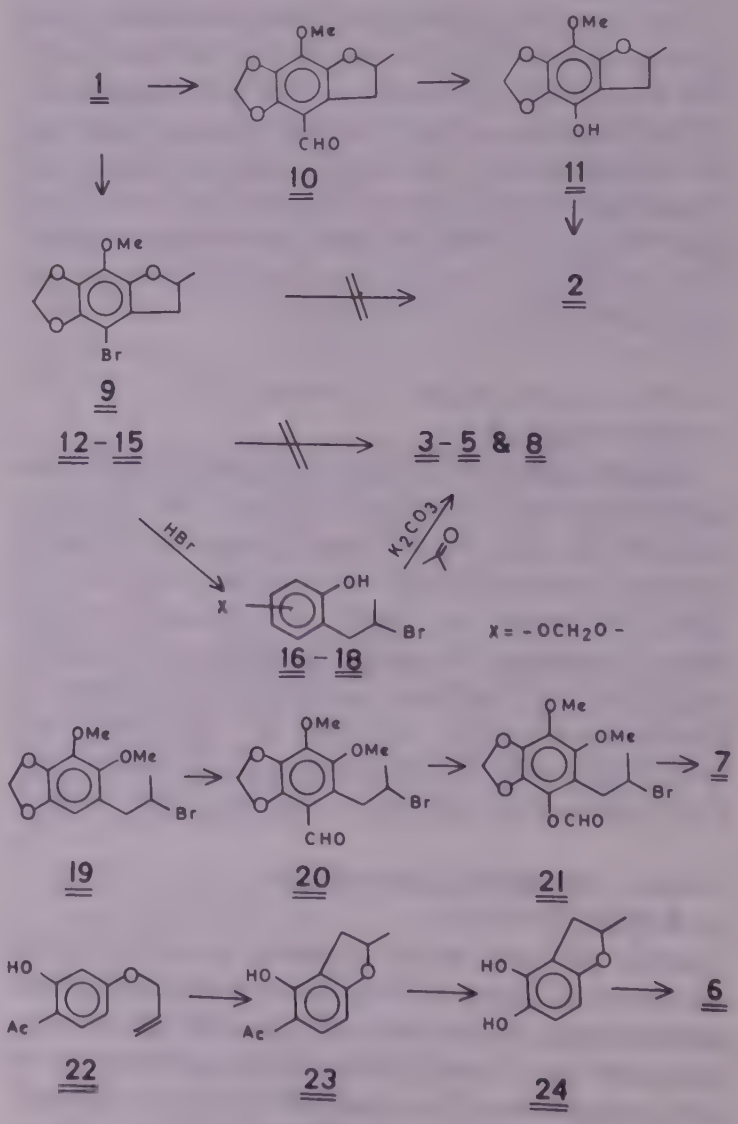
The synthesis of seven new analogues of furapiole (**1**; 6,7-dihydro-4-methoxy-6-methylfuro [2, 3, *f*]-1,3-benzodioxole) is described. The methoxy analogue (**2**) has been obtained by Vilsmeier formylation of **1** followed by Baeyer-Villiger oxidation and methylation. The angular analogue (**7**) of **2** has been prepared from dillapiole in four steps. 4-Allyloxy-2-hydroxyacetophenone (**22**) when refluxed in DMA-PTS medium gives the coumaran derivative **23** which on Dakin oxidation followed by methylation furnishes 4,5-dihydro-5-methylfuro [3, 2, *e*]-1,3-benzoidioxole (**6**). The synthesis of other analogues is best accomplished from the appropriate *o*-allylsesamols through HBr addition followed by Adams method of cyclisation of the intermediates. Bioassay studies have shown **2** and **3** as highly potent pyrethrum synergists.

Furapiole (**1**) is a new potent synergist for pyrethrum[1] and carbamate[2] insecticides. Its formation from dillapiole mediated by HBr involves an unusual selective demethylative cyclisation. In an earlier communication[3], we have postulated a mechanism for this reaction and supported with studies on a large number of structural variants.

The unusually high biological activity of furapiole is not easily understandable eventhough a great deal of structure-activity relationship (SAR) studies have been made on its derivatives and open chain analogues[1,4,5]. Since furapiole (**1**) is the first example of a methylenedioxy-α-methyldihydrobenzofuran in literature, it was of interest to synthesise its novel analogues. In this paper, we report the syntheses and synergistic efficacy of some of its analogues (**2-8**).



The synthesis of 6,7-dihydro-4,8-dimethoxy-6-methylfuro [2,3-*f*]-1,3-benzodioxole (**2**) was accomplished from furapiole (**1**) (Scheme 1). Bromination of **1** gave the bromofurapiole **9** in a quantitative yield. Attempts to convert **9** into **2** by direct methoxylation using sodium methoxide either in DMF containing



SCHEME 1

†Contribution No. 308 from the Division of Agricultural Chemicals.

Cu_2I_2[6] or by the recent procedure of Manchand *et al.*[7] employing Cu_2Cl_2-pyridine-methanol under reflux, failed. In an indirect approach, Vilsmeier formylation of **1** using N-methylformanilide-$POCl_3$ complex gave the formylfurapiole **10** in 60% yield. The presence of formyl group in **10** was indicated by its IR absorption at 1670 cm^{-1} and a one-proton singlet at δ 10.0 in its PMR spectrum in which the chemical shifts of OCH_3 and $-OCH_2O-$ protons appeared downfield by δ 0.1 in comparison to those in **1**. Baeyer-Villiger oxidation of the aldehyde **10** by performic acid afforded the phenol **11** in 50% yield, methylation of which furnished the analogue **2** in a quantitative yield. The PMR spectrum of **2** showed a six-proton singlet at δ 3.90 for the two methoxyls in accordance with the structure **2**.

The syntheses of the analogues **3-5** and **8** were achieved by elaboration of dihydrofuran ring from the corresponding benzodioxoles. The synthetic approach as outlined in Scheme 1 involved HBr addition to the corresponding *o*-allylsesamols (**12-15**) to give the *o*-(2'-bromopropyl)-sesamols (**16-18**) as intermediates followed by Adams method of base catalysed cyclisation of the latter to the dihydrofurans. While the known allylphenols (**12-15**) were prepared by the reported procedure[8,9], the new phenols (**13** and **14**) were obtained by Claisen migration of the corresponding allyloxybenzodioxoles[5]. Attempts to induce direct cyclisation of **12-15** by Adams method did not succeed due to the facile fission of methylenedioxy group under HBr-AcOH treatment. However, the methylenedioxy group was stable upto 2 hr in the presence of dry HBr in non-polar solvents such as $CHCl_3$ and the indirect route as proposed in Scheme 1 was, therefore, preferred. The bromophenols (**16-18**) thus obtained, on refluxing with acetone-K_2CO_3 furnished the required analogues **3-5** and **8** respectively in 80-85% yields. The usual method of heating **16-18** with pyridine, on the other hand, gave mixtures containing *o*-(1-propenyl)-phenols due to dehydrobromination in addition to the desired cyclised products.

A combination of the above two approaches enabled the synthesis of the angular methoxy analogue (**7**) as depicted in Scheme 1. While the treatment of dillapiole with dry HBr gave a mixture of **1** and the bromopropyl derivative (**19**) in $CHCl_3$, it exclusively led to **19** in DMF medium[3]. Formylation of **19** as in the case of **1** gave the bromoaldehyde (**20**) in about 40% yield. Performic acid oxidation of **20** gave the formyl ester (**21**) which on refluxing with acetone-K_2CO_3 underwent ester cleavage and intra-molecular cyclisation with the side chain, leading to the formation of **7**. The PMR spectrum of **7** showing two singlets of three protons each at δ 3.75 and 3.93 established the angular fusion of furan ring.

4,5-Dihydro-5-methylfuro [3,2-*e*]-1,3-benzodioxole (**6**) was synthesised through a route shown in Scheme 1. *o*-Hydroxyallylacetophenone[10] (**22**) on refluxing in N,N-dimethylaniline containing *p*-toluenesulfonic acid underwent a single-pot Claisen rearrangement and cyclisation to the coumaran **23** in 60% yield. Dakin oxidation of **23** gave the catechol **24** in about 30% yield. The poor yield of **24** was due to the formation of a mixture of polar products. A re-scanning of literature at this point revealed that 5-hydroxy-2,3-dihydrobenzofurans of this type are highly unstable in the presence of alkaline H_2O_2, their most characteristic reaction being facile oxidation to quinones with the fission of the heterocyclic ring[11]. Methylenation of **24** with CH_2Cl_2 and KF in anhyd. DMF medium[12] gave the analogue **6** in 60% yield. A comparison of its PMR spectrum with that of **3** revealed the presence of double doublets for two *ortho*-protons at δ 6.45 and 6.55 in **6** in contrast to double singlets at 6.2 and 6.4 for two *para*-protons in **3**.

The bioassay studies of **2-10** as pyrethrum synergists against red flour beetles (*Tribolium casteneum* Herbst) using our earlier technique[5] have shown that the linear analogues **1-3** are highly active, the respective factors of synergism being 5.2, 6.3 and 4.6. It implies that furo [2,3-*f*]-1,3-benzodioxoles are *per se* better pyrethrum synergists than simple 1,3-benzodioxoles, and additional methoxy substituents have an enhancing effect on this ring system as observed in other cases[4,5].

Experimental Procedure

IR spectra of all new compounds were recorded on a Perkin-Elmer-457 infrared grating spectrophotometer (ν_{max} in cm^{-1}), and PMR spectra on a Varian EM-360 60 MHz instrument using TMS as internal reference. (chemical shifts in δ, ppm). All m.ps and b.ps are uncorrected.

8-Bromo-4-methoxy-6-methyl-6,7-dihydrofuro[2,3-*f*]*-2,3-benzodioxole* (**9**)

Bromine (0.1 ml) in $CHCl_3$ (20 ml) was added dropwise to a solution of furapiole (**1**; 415 mg) in $CHCl_3$ (20 ml) till the pale yellow colour of bromine persisted. After 1 hr, the solvent was evaporated and the residue (560 mg) crystallised from methanol to give colourless needles of **9**, m.p. 59° (Found: C, 45.9; H, 3.8. $C_{11}H_{11}BrO_4$ requires C, 46.0; H, 3.9%); PMR (CCl_4): 1.46 (*d*, J = 7.5 Hz, 3H, $-CHCH_3$), 3.26 (*dq*, J = 8 Hz, 2H, benzylic), 3.96 (*s*, 3H, OCH_3), 5.0 (*m*, 1H, C*H*-Me), 5.92 (*s*, 2H, OCH_2O).

8-Formyl-4-methoxy-6-methyl-6,7-dihydrofuro[2,3-*f*]*-1,3-benzodioxole* (**10**)

N-Methylformanilide (11.2 g) was mixed dropwise with $POCl_3$ (11.5 g) in dry chlorobenzene (10 ml) at 0°.

After keeping for 1 hr, the mixture was added to furapiole (1; 10.6 g) in chlorobenzene (20 ml) at 0°, stirred at 20° for 6 hr and heated at 60-70° for 8 hr. It was then poured into ice-water (100 ml), the organic layer washed free of acid and dried over anhyd. Na_2SO_4. Dilution of the organic layer with hexane followed by chilling precipitated the aldehyde (**10**) which was recrystallised from hexane-benzene (95:5) as light yellow needles (7.1 g), m.p. 101-2° (Found: C, 60.9; H, 5.0. $C_{12}H_{12}O_5$ requires C, 61.0; H, 5.1%); IR ($CHCl_3$): 1670 (C=O); PMR (CCl_4): 1.46 (*d*, J = 7.5 Hz, 3H, $-CHCH_3$), 4.10 (*s*, 3H, OCH_3), 5.0 (*m*, 1H, $-CHCH_3$), 6.0 (*s*, 2H, OCH_2O), 10.0 (*s*, 1H, CHO).

6,7-Dihydro-4-methoxy-6-methylfuro[2,3-*f*]-1,3-*benzodioxol-8-ol* (**11**)

Baeyer-Villiger oxidation of **10** (4.72 g) with performic acid using the procedure described for sesamol[5] gave the phenol **11** which was crystallised from cyclohexane as white plates (2.35 g), m.p. 89-90° (Found: C, 58.8; H, 5.3. $C_{11}H_{12}O_5$ requires C, 58.9; H, 5.4%); IR ($CHCl_3$): 3550; PMR ($CDCl_3$): 1.46 (*d*, J = 7.5 Hz, 3H, $-CHCH_3$), 2.91 (*dq*, J = 7.5 Hz, 2H, benzylic), 3.92 (*s*, 3H, OCH_3), 4.62 (br, *s*, 1H, OH), 5.0 (*m*, 1H, $-CHCH_3$), 5.84 (*s*, 2H, OCH_2O).

6,7-Dihydro-4,8-dimethoxy-6-methylfuro-[2,3-*f*]-1,3-*benzodioxole* (**2**)

Methylation of the above phenol (**11**; 1.12 g) with MeI (1.5 ml) in dry acetone (50 ml) containing anhyd. K_2CO_3 (1.4 g) under reflux for 4 hr furnished the methoxyfurapiole (**2**; 1.10 g) which was recrystallised from MeOH as white needles, m.p. 47° (Found: C, 60.3; H, 5.8. $C_{12}H_{14}O_5$ requires C, 60.5; H, 5.9%); PMR ($CDCl_3$): 1.45 (*d*, J = 7.5 Hz, 3H, $-CHCH_3$), 2.98 (*dq*, J = 7.5 Hz, 2H, benzylic), 3.94 (*s*, 6H, 2 × OCH_3), 5.0 (*m*, 1H, $-CHCH_3$), 5.84 (*s*, 2H, OCH_2O).

6-(2′-*Bromopropyl*)-4,5-*dimethoxy*-1,3-*benzodioxole* (**19**)

Dillapiole [4,5-Dimethoxy-6-(2′-propenyl)-1,3-benzodioxole] (11.1 g, 0.05 mol) in dry DMF (100 ml) was saturated with dry HBr at 0°. After keeping for 2 hr, it was poured into ice-cold water (300 ml), extracted with $CHCl_3$, washed the org. layer with H_2O till neutral, dried over anhyd. Na_2SO_4 and evaporated to furnish the bromopropyl derivative (**19**, 14.9 g). It was passed through a short column of silica gel (100 g) using hexane-benzene (4:1) as eluent to give **19** as a light brown oil (Found: C, 47.3; H, 4.9. $C_{12}H_{15}BrO_4$ requires C, 47.5; H, 5.0%); PMR (CCl_4): 1.30 (*d*, J = 8 Hz, 3H, $CHBrCH_3$), 2.75 (*dd*, J = 7 Hz, J = 3 Hz, 2H, benzylic), 3.75, 3.95 (each *s*, 6H, 2 × OCH_3), 5.14 (*m*, 1H, $-CHBr$), 5.8 (*s*, 2H, OCH_2O), 6.21 (*s*, 1H, Ar-*H*).

6-(2′-*Bromopropyl*)-4,5-*dimethoxy*-7-*formyl*-1,3-*benzodioxole* (**20**)

Vilsmeier formylation of **19** (0.025 mole) by the procedure described for **10** furnished the bromoaldehyde **20** in 40% yield. It was recrystallised from *n*-hexane as pale yellow needles, m.p. 91° (Found: C, 46.9; H, 4.4. $C_{13}H_{15}BrO_5$ requires C, 47.2; H, 4.6%); IR (CCl_4): 1675 (C=O); PMR (CCl_4): 1.32 (*d*, J = 8 Hz, 3H, $-CHBrCH_3$), 2.85 (*dd*, J = 7 Hz, J = 3.5 Hz, 2H, benzylic protons), 3.75, 4.10 (each *s*, 6H, 2 × OCH_3), 5.15 (*m*, 1H, $-CHBr$-), 6.0 (*s*, 2H, OCH_2), 10.2 (*s*, 1H, CHO).

6-(2′-*Bromopropyl*)-4,5-*dimethoxy*-7-*formyloxy*-1,3-*benzodioxole* (**21**)

The above aldehyde (**20**; 6.62 g) was oxidized with performic acid at −5° for 16 hr as described earlier for **11**. The formic acid solution of the product was poured into ice-water, extracted with diethyl ether, dried over anhyd. Na_2SO_4 and solvent removed to furnish the formyl ester (**21**; 2.1 g) as a reddish brown oil. Its purity was ascertained by TLC (Found: C, 44.5; H, 4.1. $C_{13}H_{15}BrO_6$ requires C, 45.0 + H, 4.4%); IR ($CHCl_3$): 1740 (ester C = O); PMR ($CDCl_3$): 1.35 (*d*, J = 7.5 Hz, 3H, $CHCH_3$), 3.05 (*dd*, 2H, benzylic protons), 3.72, 3.93 (each *s*, 6H, 2 × OCH_3) 5.10 (*m*, 1H, $-CHBr-$), 5.89 (*s*, 2H, OCH_2O), 7.95 (*s*, 1H, $HCOO-$).

5,6-Dihydro-7,8-dimethoxy-5-methylfuro-[2,3-*e*]-1,3-*benzodioxole* (**7**)

The formyl ester (**21**; 1.04 g) was refluxed in dry acetone (50 ml) containing anhyd. K_2CO_3 (0.5 g) on a water bath for 6-8 hr. The completion of the reaction was monitored by TLC. The usual work-up gave a residue (650 mg) which was purified on a column of silica gel (20 g) using hexane-benzene (3:1) as eluent to give **7** as white needles, m.p. 39-40° (Found: C, 60.4; H, 5.9. $C_{12}H_{14}O_5$ requires C, 60.5 + H, 5.9%); PMR ($CDCl_3$): 1.49 (*d*, J = 8 Hz, 3H, $CHCH_3$), 2.96 (*dq*, J = 7.5 Hz, 2H, benzylic protons), 3.75, 3.93 (each *s*, 6H, 2 × OCH_3), 5.02 (*m*, 1H, $-CHCH_3$), 5.82 (*s*, 2H, OCH_2O).

2-Allyl-4,5-methylenedioxyphenol[8] (**12**) and 6-allyl-2,3-methylene-dioxyphenol[9] (**15**) were prepared as described earlier.

o-Allylphenols (**13** and **14**)

These were prepared by the Claisen rearrangement of 5-allyloxy-6-methoxy-1,3-benzodioxole and 6-allyloxy-4,5-dimethoxy-1,3-benzodioxole as reported earlier[5]. The corresponding allyloxybenzodioxoles (10 mmol) in N,N-dimethylaniline (20 ml) were refluxed

for 2 hr, cooled and poured into ice-cold dil. HCl (100 ml, 1:1). Usual work-up followed by vacuum distillation gave **13** or **14** as a pale yellow viscous liquid (yield 55%).

4-(2′-Propenyl)-6-methoxy-1,3-benzodioxol-5-ol (**13**): b.p. 115-16°/1 mm (Found: C, 63.1; H, 5.6. $C_{11}H_{12}O_4$ requires C, 63.5; H, 5.8%).

4-(2′-Propenyl)-6,7-dimethoxy-1,3-benzodioxol-5-ol (**14**): b.p. 124-25°/1 mm (Found: C, 60.1; H, 5.7. $C_{12}H_{14}O_5$ requires C, 60.5; H, 5.9%).

The above *o*-allylphenols gave the following common spectral data: IR ($CHCl_3$): 3550(OH), 900 (=CH_2); PMR ($CDCl_3$): 3.25 (*d*, $J=8$ Hz, benzylic protons), 4.95 (*m*, 2H, =CH_2), 5.8 (*m*, 1H, CH=), 5.5-6.0 (br, *s*, 1H, OH).

Reaction of o-allylphenols (**12-15**) *with HBr-AcOH*

A typical example is described below:

Aqueous HBr (48%, 0.2 ml) was added to a solution of the phenol **12** (100 mg) in gl. AcOH (1 ml) till the whole mixture became turbid. The mixture was warmed on a water-bath for 30-45 min at 50-60°, diluted with water (10 ml) and fractionated into phenolic and neutral portions. The latter portion amounted to hardly 5% while the phenolic part was mostly polymeric in nature and contained only traces of the starting phenol (**12**). Variation in reaction period and temperature also did not help in inducing cyclisation of allylphenols. For example, the phenol **12** could be recovered as such following the above treatment at 0° for 1 hr as well as keeping the reaction mixture at room temperature for 1/2 hr.

Reaction of o-allylphenols (**12-15**) *with dry HBr*

A solution of appropriate *o*-allylphenol (1 mmol) in dry $CHCl_3$ (15 ml) at 0° was saturated with HBr. After keeping for 2 hr, the reaction mixture was poured into ice-water (50 ml), the $CHCl_3$ layer washed with water till neutral, dried (Na_2SO_4) and evaporated to furnish the corresponding *o*-(2′-bromopropyl)phenol in $\geq 95\%$ yield as a dark brown liquid. The *o*-allylphenols, thus prepared, showed IR absorption at 3550 (br, OH) and 3400 (bonded OH), and characteristic PMR signals at 1.65 (*d*, $J=7.5$ Hz, 3H, $CHBrCH_3$), 3.15, 3.20 (*d*, $J=7.5$ Hz, 2H, benzylic protons), 4.3-4.5 (*m*, 1H, $-CHBrCH_3$), 4.5-5.7 (br *s*, 1H, OH). They were used as such without further purification in the following reaction.

Preparation of furapiole analogues (**3-5** and **8**)

o-(2′Bromopropyl)phenols (1 mmol each) were refluxed separately in dry acetone (50 ml) containing anhyd. K_2CO_3 (140 mg, 1 mmol) on a water-bath for 5-8 hr and worked-up as described in the case of **2** to furnish the corresponding furapiole analogues in 80-85% yields. Their characterization data are as follows:

6,7-Dihydro-6-methylfuro[2,3-*f*]-1,3-benzodixole (**3**): Colourless oil (Found: C, 67.3; H, 5.6. $C_{10}H_{10}O_3$ requires C, 67.4; H, 5.7%); PMR (CCl_4): 1.50 (*d*, $J=8$ Hz, 3H, $CHCH_3$), 2.8 (*dq*, $J=7.5$ Hz, 2H, benzylic protons), 4.85 (*m*, 1H, $-CHCH_3$), 5.80 (*s*, 2H, OCH_2O), 6.21 (*s*, 1H, Ar-*H*), 6.45 (*s*, 1H, Ar-*H*). 4,5-Dihydro-7-methoxy-5-methylfuro[3,2-*e*]-1,3-benzodioxole (**4**): Pale yellow oil (Found: C, 63.4; H, 5.7. $C_{11}H_{12}O_4$ requires C, 63.5; H, 5.8%). PMR (CCl_4): 1.52 (*d*, $J=7.5$ Hz, 3H, $-CHCH_3$), 2.72 (*dq*, $J=7.5$ Hz, 2H, benzylic protons), 3.75 (*s*, 1H, OCH_3), 4.92 (*m*, 1H, $-CHCH_3$), 5.83 (*s*, 2H, OCH_2O), 6.08 (*s*, 1H, Ar-*H*).

4,5-Dihydro-7,8-dimethoxy-5-methylfuro [3,2-*e*]-1,3-benzodioxole (**5**): It was crystallised from MeOH as white plates, m.p. 38-39° (Found: C, 60.3; H, 5.8. $C_{12}H_{14}O_5$ requires C, 60.5; H, 5.9%); PMR ($CDCl_3$): 1.46 (*d*, $J=7.5$ Hz, 3H, $CHCH_3$), 2.96 (*dq*, $J=7.5$ Hz, 2H, benzylic protons), 3.75, 3.92 (each *s*, 6H, 2 $\times OCH_3$), 5.02 (*m*, 1H, $-CHCH_3$), 5.80 (*s*, 2H, OCH_2O).

5,6-Dihydro-5-methylfuro [2,3-*e*]-1,3-benzodioxole (**8**): Colourless oil (Found: C, 67.2; H, 5.6. $C_{10}H_{10}O_3$ requires C, 67.4. H, 5.7%); PMR (CCl_4): 1.45 (*d*, $J=7$ Hz, $-CHCH_3$), 2.92 (*dq*, $J=7$ Hz, 2H, benzylic protons), 4.95 (*m*, 1H, $-OCH$-Me), 5.80 (*s*, 2H, OCH_2O), 6.41, 6.65 (each *s*, 1H each, Ar-*H*).

5-Acetyl-2,3-dihydro-4-hydroxy-2-methylbenzofuran (**23**):

4-Allyloxy-2-hydroxyacetophenone[10] (**22**; 3.8 g) was refluxed in dry N,N-dimethylaniline (40 ml) fortified with anhyd. *p*-toluenesulfonic acid (3 g) for 4 hr and 90% of the aniline distilled off. The residue after cooling to room temperature was poured into ice-water (50 ml) containing conc. HCl (10 ml) and worked-up as usual to give **23** as a colourless viscous oil which solidified immediately into white plates (2.3 g), m.p. 44-45° (Found: C, 68.6; H, 6.2. $C_{11}H_{12}O_3$ requires C, 68.7; H, 6.3%); IR (KBr): 3470 (OH), 1695 (C=O); PMR ($CDCl_3$): 1.45 (*d*, $J=7$ Hz, 3H, $CHCH_3$), 2.45 (*s*, 3H, $COCH_3$), 2.97 (*dq*, $J=7.0$ Hz, 2H, benzylic protons), 5.05 (*m*, 1H, $-OCH-$), 6.27, 7.53 (each *s*, 1H, each Ar-*H*), 12.63 (*s*, 1H, OH).

2,3-Dihydro-4,5-dihydroxy-2-methylbenzofuran (**24**)

A solution of **23** (1.92 g) in aq. NaOH (10 ml, 1*N*) was treated with aq. H_2O_2 (10 ml, 6%) at 0° under nitrogen atmosphere. The initial precipitate formed gradually went into solution and after 45 min the reaction mixture was quenched with 2*N* HCl (10 ml), cooled and the dark coloured precipitate (0.65 g) filtered. It was

purified by repeated crystallisation from acetone-hexane (1 : 3) to give **24** as cream coloured plates (330 mg), m.p. 125-6°; gave positive colour reaction with $FeCl_3$ (Found: C, 64.9; H, 5.8. $C_9H_{10}O_3$ requires C, 65.0; H, 6.0%); IR (KBr): 3500-3600 (br, OH).

4,5-Dihydro-5-methylfuro [3,2-*e*]-1,3-*benzodioxole* (**6**)

Methylenation of **24** (250 mg) in dry DMF (10 ml) containing anhyd. KF (450 mg) with CH_2Cl_2 (0.1 ml) by the general procedure[12] gave a pale yellow oil (150 mg) which was chromatographed over silica gel (3 g) using hexane-C_6H_6 (4:1) as eluent to give **6** as a colourless oil (95 mg) (Found: C, 67.3: H, 5.5. $C_{10}H_{10}O_3$ requires C, 67.4; H, 5.7%); PMR (CCl_4): 1.46 (*d*, $J=7.5$ Hz, 3H, $-CHCH_3$), 2.78 (*dq*, $J=7$ Hz, 2H, benzylic protons), 4.96 (*m*, 1H, $-OCH-$), 5.82 (*s*, 2H, OCH_2O), 6.46 (each *s*, 1H each, Ar-*H*).

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Notes

Structure of Hypericorin†

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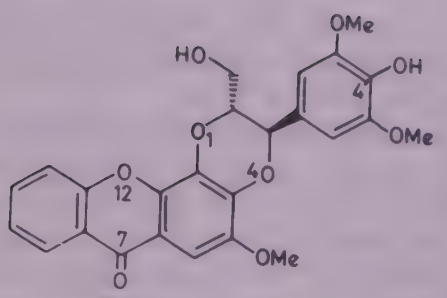
Hypericorin, a new xanthonolignoid isolated from *Hypericum mysorense* Heyne has been assigned the structure as *trans*-(±)-2,3-dihydro-3-(3,5-dimethoxy-4-hydroxyphenyl)-2-(hydroxymethyl)-5-methoxy-7*H*-1, 4-dioxino[2,3-*c*]xanthen-7-one (**1**) on the basis of spectral and chemical studies.



(1)

As a part of our continuing interest on the constituents of the ethyl acetate fraction of the aerial parts of *Hypericum mysorense* Heyne (Hypericaceae), we now wish to report the isolation and characterisation of a new xanthonolignoid, hypericorin.

Hypericorin (**1**), $C_{25}H_{22}O_9$ (M^+, 466) was crystallised from ethyl acetate in colourless needles, m.p. 262°. The UV spectrum in methanol (210, 250 and 320 nm), IR spectrum in KBr (3350, 1640 and 1600 cm^{-1}) and mass spectrum were indicative of a xanthonolignoid skeleton[1,2] in **1**. The formation of a monomethyl ether (M^+, 480) and a diacetate (M^+, 550) indicated the presence of one phenolic and one alcoholic function in the molecule. The nature of alcoholic group as primary was supported by the PMR spectrum of **1** (DMSO-d_6), which displayed besides the CH_2 and OH protons at δ 4.20 and 8.72 respectively, signals at δ 3.78, 3.80 and 3.90 assignable to methoxyl protons. The presence of *trans*-1,4-dioxane ring system was indicated by the doublets ($J = 8.0$ Hz) at δ 5.53 and 4.94.

When **1** was treated with anhyd $AlCl_3$ in benzene, it afforded 2,3,4-trihydroxyxanthone as one of the major products, identified by direct comparison of its trimethyl ether with the authentic sample[3]. Thus 2,3,4-trihydroxylation pattern of xanthone nucleus was evident in **1**. The appearance of strong M^+, $M^+ - 15$ and $M^+ - 30$ ions in the mass spectrum excluded the possibility of methoxyl group being at 12b-position of dioxinoxanthone skeleton[4], indicating that C-3 and C-4 hydroxyls of the xanthone moiety are involved in the formation of 1,4-dioxane ring. Intense peaks at *m/z* 154, 167 and 210 in the mass spectrum of **1**, suggested that the lignan part of **1** contains a trisubstituted phenyl ring. Another conclusion drawn from the mass spectral data was the tentative attachment of aryl and hydroxymethyl substituents at C-3 and C-2 positions of dioxane ring respectively. The exact orientation of aryl moiety was found to be 3,5-dimethoxy-4-hydroxyphenyl on the basis of PMR spectrum and deuteriation experiment. The PMR spectrum of **1** had a two-proton singlet at δ 6.7, assignable to the C-2 and C-6 protons of trisubstituted aryl ring. No deuterium could be incorporated on treatment of **1** with D_2O/KOH in a sealed tube, showing that there were no protons, *ortho* and *para* to phenolic hydroxyl group, available for desired electrophilic substitution by deuterium.

The regiospecific placement of 3,5-dimethoxy-4-hydroxyphenyl and hydroxymethyl groups was ascertained by alkaline hydrolysis[2] of **1**. Treatment of **1** with aq NaOH led to the opening of dioxane ring between 3- and 4-positions of dioxinoxanthone, initiated jointly by *para*-phenolic group in the aryl moiety and carbonyl of xanthone nucleus. Hence 3,5-dimethoxy-4-hydroxyphenyl and hydroxymethyl groups were placed at C-3 and C-2 positions respectively.

All the physical and chemical data led to the assignment of **1** as *trans*-(±)-2,3-dihydro-3-(3,5-dimethoxy-4-hydroxyphenyl)-2-(hydroxy-

Table 1—CMR Data of Hypericorin

Carbon	Chemical shifts in δ, ppm	Carbon	Chemical shifts in δ, ppm
C-2	76.40	C-11a	155.14
C-3	77.67	C-12a	141.09
C-4a	139.45	C-12b	132.34
C-5	145.70	C-1′	132.34
C-6	96.66	C-2′	105.92
C-6a	120.61	C-3′	147.90
C-7	174.48	C-4′	147.98
C-7a	113.83	C-5′	147.90
C-8	125.59	C-6′	105.92
C-9	123.86	CH_2OH	59.82
C-10	134.34	OMe at C-5	55.65
C-11	117.74	Ome at C-3′	56.15
		OMe at C-5′	56.15

†CDRI Communication No. 3828.

methyl)-5-methoxy-7*H*-1,4-dioxino[2,3-*c*]xanthen-7-one.

The CMR spectrum of **1** was taken on a Bruker WM 400 MHz FT NMR spectrometer operating at 100.13 MHz. Each carbon was assigned on the basis of SFORD and decoupled experiments and the chemical shift values are given in Table 1.

The decoupling of aromatic protons leaves the C-4a and C-12b signals as singlets, indicating their weak intereaction with H-2 and H-3 of dioxane ring. Therefore the latter are perpendicular to the plane of xanthone nucleus, i.e. in a *trans*-diaxial relationship, in accordance with PMR spectral data. Further support for this assignment was available from the ^{13}C chemical shifts of C-2, C-3 and C_2-CH_2OH groups. They were in good agreement with those reported for eusiderin[5].

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Garcinone-D, a New Xanthone from *Garcinia mangostana* Linn.

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Garcinone-D, another new minor xanthone has been isolated from the fruit hulls of *Garcinia mangostana* Linn. It has been assigned structure (I) on the basis of spectral data and chemical correlation.

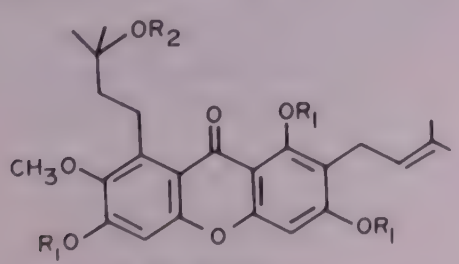
We have previously reported[1-4] the isolation and structure elucidation of several new minor xanthones from *Garcinia mangostana* Linn. In addition Govindachari *et al.*[5] have reported the isolation of other polyoxygenated xanthones, some of which appear to be putative biogenetic precursors of the minor xanthones.

All these polyoxygenated xanthones bear one or two C_5-unit side chains either as uncyclised 3-methyl-but-2-enyl moiety or as linearly or angularly cyclised pyran ring except in the case of garcinone-C where a 3-hydroxy-3-methylbutanyl substitution is present. In this note is reported the isolation and structure elucidation of another new minor xanthone having the 3-hydroxy-3-methylbutanyl side chain.

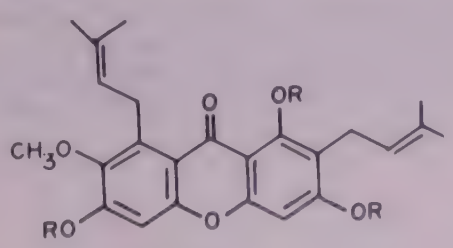
Dried and powdered well-ripe fruit hulls of *G. mangostana* were successively extracted with the solvents of increasing polarity. The chloroform extract on chromatographic separation afforded the new minor xanthone, designated as garcinone-D, along-with garcinones-A to C[4].

Garcinone-D (I), $C_{24}H_{28}O_7$, crystallised from methanol as light yellow needles, m.p. 202-4°; UV (EtOH): 244, 260 (sh), 323 and 362 nm (log ε 4.5, 4.1, 4.4 and 4.4); + NaOAc : 244, 259 (sh) and 364 nm (log ε 4.5, 4.1 and 4.2); IR (nujol): 3400 (free OH), 3250 (chelated OH), 1645, 1610, 1560, 1380, 1340, 1305, 1280, 1230, 1205, 845 and 820 cm^{-1}; MS : *m/z* 428 (25), 410 (25), 395 ($M-H_2O-Me$, 7), 393 (7), 367 ($M-H_2O-Me-CO/M-H_2O-C_3H_7$, 40), 355 ($M-H_2O-55$, 42), 354 ($M-H_2O-56$, 37), 339 ($M-H_2O-C_3H_7-CO/M-H_2O-Me-2\times CO$, 100), 313 (46), 297 (23) and 285 (12); PMR (DMSO-d_6) : δ 13.25 (1H, *s*), 6.85 (1H, *s*), 6.41 (1H, *s*), 5.15 (1H, *t*, J = 6.5 Hz), 3.85 (3H, *s*), 3.38 (6H, *m*), 1.60 (3H, *s*), 1.68 (3H, *s*) and 1.22 (6H, *s*). The two three-proton singlets which appeared at δ 1.60 and 1.68 were assigned to two methyls of prenyl side chain whereas the hydroxylated side chain methyls appeared at 1.22, being shifted upfield[4]. The C_7-OMe appeared at 3.85 and the double bonded methine of the side chain appeared at 5.15 as a one-proton triplet. The absence of any benzylic proton pair in the region 4.1-4.3 and the appearance of a six-proton multiplet at 3.38 indicates that the C-8 substituted side chain is the hydroxylated one. The chelated aromatic hydroxyl at C-1 appeared at 13.25 and the two aromatic proton singlets appeared at 6.85 (5-H) and 6.41 (4-H), the latter being in the electron-rich phloroglucinol ring is shifted upfield.

Garcinone-D on acetylation (Ac_2O/Py, 12 hr) afforded the fully acetylated tetraacetate (II) as white needles, m.p. 112-14°; IR (nujol) 1765, 1730 and 1245 cm^{-1}; MS : *m/z* 596(6), 536 ($M-CH_3COOH$, 20), 494 ($M-CH_3COOH-CH_2CO$, 40), 452 ($M-60-2\times 42$, 52), 410 ($M-60-3\times 42$, 45), 367 (52), 355 (38) and 353 (100). However, on acetylation with Ac_2O/Py by heating on a boiling water-bath for 2 hr, garcinone-D afforded the partially acetylated product, tri-O-acetylgarcinone-D (III) after preparative TLC followed by crystallisation from pet ether-benzene as colourless needles; m.p. 128-30°; MS : *m/z* 554 (M^+, 15), 536 ($M-H_2O$, 10), 512 (25), 494 (6), 470 (60) and 428 (100). Compound (III) on dehydration with $POCl_3$/Py (room temp., overnight) produced tri-O-acetylmangostin (IV) as a white solid, m.p. 120-21°, which on saponification (5% methanolic KOH) afforded mangostin (V), the major yellow pigment of



I $R_1 = R_2 = H$
II $R_1 = R_2 = Ac$
III $R_1 = Ac, R_2 = H$



IV R = Ac
V R = H

the plant as yellow amorphous solid, m.p. 177-79°, identical (m.m.p., co-TLC and IR) with an authentic sample. All these observations lead to structure (I) for garcinone-D.

It should be mentioned here that garcinone-C and garcinone-D are probably the first two naturally occurring xanthones with a 3-hydroxy-3-methylbutanyl side chain, although flavones having this side chain are already known[6]. However, a report[7] of xanthones with 4-hydroxy-3-methylbutanyl side chain in a plant belonging to the same family *Guttiferae* is interesting from biogenetic and chemotaxonomic points of view.

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Synthesis of Some New Arylnaphthaquinones Using Palladium Acetate in Acetic Acid

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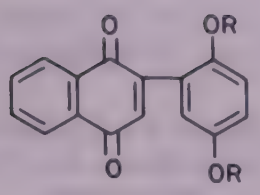
A one-step synthesis of some new 2-aryl-1,4-naphthaquinones (**1-3**) by aryl substitution on 1,4-naphthaquinone and substituted naphthaquinone using palladium acetate in acetic acid is reported.

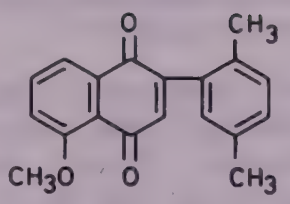
Aryl substituted naphthaquinones are good anticoccidial agents in poultry industry[1]. In an earlier paper from our laboratory, a one-step arylation of 1,4-naphthaquinones using $PdCl_2$ in fused sodium acetate and acetic acid system[2] was reported for the first time. Subsequently, the syntheses of arylnaphthaquinones were reported with improved yields using $Pd(OAc)_2$ in acetic acid[3]. We present in this note, syntheses of new arylnaphthaquinones (**1** and **2**) in good yields by nucleophilic substitution of 1,4-naphthaquinone using palladium acetate in acetic acid. Arylation of juglone methyl ether led to a inseparable mixture of positional isomers, 2- and 3-(2′-5′-dimethylphenyl)juglone methyl ethers (**3a** and **3b**).

In a typical procedure, equimolar amounts (2 mmol each) of palladium acetate and 1,4-naphthaquinone were heated at 80°C for 8 hr with arylating agents (6 mmol) in acetic acid (10 ml). The precipitated palladium metal was filtered, the filtrate diluted with water and extracted with ether. The ether extract was evaporated and the residue was chromatographed on silica gel. The characterisation data of various arylnaphthaquinones obtained are as follows:

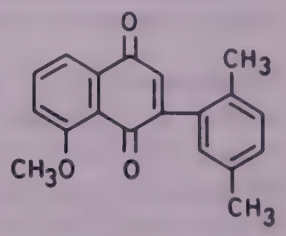
2-(2′,5′-Dimethoxyphenyl)-1,4-naphthaquinone (**1**): yield 70%; m.p. 98°; MS: *m/z* 294(100), 279(60), 251(38), 236(18), 208(19), 180(25), 133(8), 105(18), 104(56), 76(67); IR(KBr): 1652 cm^{-1} (ν C=O); PMR($CDCl_3$): δ 3.76 and 3.82 (each *s*, 3H each, two methoxyls), 7.0(1H, *s*, olefinic proton), 6.8(1H, *d*, J = 2Hz, *meta*-coupled C_6-H), 6.92(2H, *d*, C_3- and C_4-protons) and 7.75(2H, *m*) and 8.08(2H, *m*, of quinone protons) (Found: C, 73.7; H, 4.6. $C_{18}H_{14}O_4$ requires C, 73.5; H, 4.8%).



1 = R = CH_3
2 = R = C_2H_5



3a



3b

2-2′,5′-Diethoxyphenyl)-1,4-naphthaquinone (**2**): yield 72%; m.p. 92°; MS: *m/z* 322(100), 294(58), 266(52), 238(40), 210(28), 133(10), 105(21), 104(37), 76(55); IR(KBr): 1652 cm^{-1} (ν C=O); PMR($CDCl_3$): δ 1.31 (6H, *m*, two methyls), 3.61(4H, *q*, two methylene protons of the two ethoxy groups), 7.0(1H, *s*, olefinic proton), 6.82(1H, *d*, *meta*-coupled C_6-H), 6.90(2H, *d*, $C_{3'}$ and $C_{4'}$ protons), 7.72 and 8.05 (each *m*, 2H each of the quinone protons) (Found: C, 75.34; H, 5.55. $C_{20}H_{18}O_4$ requires C, 74.52; H, 5.63%).

Mixture of 2- and 3-(2′,5′-Dimethylphenyl)juglone methyl ethers (**3a** and **3b**): yield 74%; PMR($CDCl_3$): δ 3.83 and 3.88 (two methoxy signals of the quinone moiety due to **3a** and **3b**), 2.08 and 2.33 (methyl protons), 6.76 (olefinic protons), 6.98(C_6-proton), 7.23(C_3- and C_4-protons) and 7.68 (remaining aromatic protons).

The author thanks Dr M Pardhasaradhi and Dr G S Sidhu for useful discussions and encouragement.

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Terminal Olefin Oxidation: A Short Synthesis of Himasecolone

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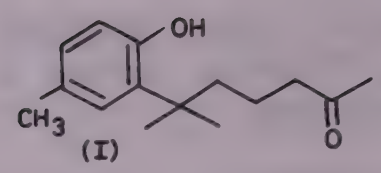
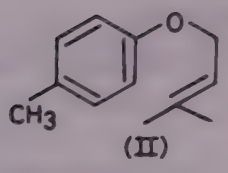
A short synthesis of himasecolone (I) is reported. *p*-Cresyl prenyl ether (II) on Claisen rearrangement gives the olefinic phenol acetate (III), Which on reaction with acetone in the presence of $Mn(OAc)_3$ yields IV. Hydrolysis of IV leads to the title compound (I).

Himasecolone (I), a phenolic sesquiterpenoid was isolated by Agarwal and Rastogi[1] from *Cedrus deodara* (Roxb.) Loud. (Pinaceae). Recently its synthesis has been reported by Ho and Hall[2]. In this note we report a relatively short synthesis of I. The key step in our approach is essentially based on the reaction of terminal olefin with organic radicals generated[3] by oxidation with $Mn(OAc)_3$. This approach was earlier utilised in the synthesis of prostanoid synthons[4,5].

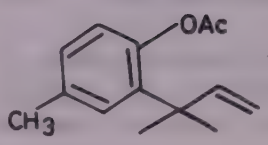
The alkylation of *p*-cresol with prenyl bromide using NaH/DMSO led to *p*-cresyl prenyl ether (II), b.p. 116-18°/5 mm. The identity of II was established by the hydroxyl band absence and presence of characteristic ether band at 1240 cm^{-1} in its IR spectrum and PMR signals at δ 1.7 and 1.8 [2*s*, $-CH=C(CH_3)_2$], 2.26 (*s*, Ar $-CH_3$), 4.48 [*d*, 2H, $-O-CH_2-CH=C(CH_3)_2$] 5.5 [*br*, *t*, $-CH_2-CH=C(CH_3)_2$] and 7.01 and 7.11 (2*d*, J = 9 Hz, 1,4-substituted Ar−H). The prenyl ether (II) was subjected to Claisen rearrangement in the presence of Ac_2O and NaOAc in a sealed tube at 200° for 24 hr. The resulting acetate (III) obtained in 35% yield exhibited characteristic IR bands at 1765, 1190 (acetate), 910 cm^{-1} ($-CH=CH_2$) and PMR signals at δ 1.42 [*s*, 6H, $C(CH_3)_2$], 2.20 (*s*, $Ar-O-CO-CH_3$), 2.35 (*S*, 3H, $Ar-CH_3$), 4.86-6.15 (*m*, $-CH=CH_2$)



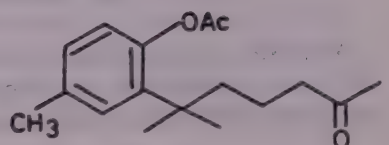
(I)



(II)



(III)



(IV)

and 6.80-7.20 (*m*, 3H, 1,2,4-trisubstituted Ar−H). Compound (III) on reaction with acetone under reflux for 24 hr in the presence of $Mn(OAc)_3$ afforded the three-carbon homologated product (IV) in 50% yield. It displayed the characteristic IR bands at 1760 and 1190 (acetate), 1715 cm^{-1} (ketone) and PMR signals at δ 2.06 (*s*, 3H, $-COCH_3$), 2.33 (*s*, 3H, $AR-O-CO-CH_3$), 2.34 (*s*, 3H, $ArCH_3$), 6.89 (*dd*, 1H, J = 9 & 2 Hz), 7.08 (*d*, 1H, J = 9 Hz) and 7.16 (*br*, *s*, 1H). Mild alkaline hydrolysis of IV resulted in the desired product (I) in almost quantitative yield. The physical and spectral (UV, IR, PMR and MS) properties of I are in good agreement with those reported[1].

One of the authors (SVT) is thankful to the Department of Atomic Energy for the award of a research fellowship.

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Dehydrohalogenation of 6-Oxo-5α-bromocholestanes: Ring-A Aromatization

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Aromatization of 6-oxo-5α-bromocholestan-3β-yl chloride (I) with dimethylformamide/LiCl leads to aromatised steroids IV, V and VI. II under similar conditions gives IV, V, VI, VII and VIII whereas III affords IV, V, VI, IX and X. The products have been characterised by their spectral properties and comparison with authentic samples where available.

In continuation of our earlier work[1] and that of others[2-5] we report herein the aromatization of 6-oxo-5α-bromocholestan-3β-yl chloride (I), 6-oxo-5α-bromocholestan-3β-yl acetate (II) and 6-oxo-5α-bromocholestan-3β-yl propionate (III) using DMF/LiCl. The aromatised steroids are recognized for wide ranging biological activities[6-10].

The ketone (I)[11] on heating under reflux with DMF/LiCl[12] gave 6-oxo-19-norcholesta-1,3,5(10)-triene (IV)[3,13] along with 6-oxocholesta-2,4-diene (V)[14] and 3,6-dioxo-5α-cholestane (VI)[15], characterised on the basis of their spectral data and in the case of V and VI by direct comparison with authentic samples.

Under similar conditions II[15] afforded IV, V, VI, 6-oxocholest-4-en-3β-yl acetate (VII)[15] and 6-oxo-5α-cholestan-3β-yl acetate (VIII)[16], while III gave IV, V, VI, 6-oxocholest-4-en-3β-yl propionate (IX) and 6-oxo-5α-cholestan-3β-yl propionate (X).

All melting points were determined on a Kofler block and are uncorrected. Petroleum ether refers to fraction, b.p. 60-80°. IR spectra (ν_{max} in cm^{-1}) were recorded in KBr on a Pye-Unicam SP3-100 spectrophotometer, UV spectra in methanol (λ_{max} in nm) on a Pye-Unicam PU 8800 spectrophotometer and PMR spectra in $CDCl_3$ on a Varian A60 D instrument with TMS as an internal standard (chemical shifts in δ-scale).

The ketone (I[11], 2 g) was dissolved in DMF (30 ml) and LiCl (500 mg) added to it. The mixture was heated under reflux for 3 hr, poured into water and extracted with ether. The ethereal layer was washed with water, aq sodium bicarbonate (5%), water and dried (Na_2SO_4). Evaporation of the solvent gave an oil which was chromatographed over silica gel (40 g). The column was successively eluted with 40:1, 35:1 and 6:1 light petroleum-ether to give three fractions respectively. Fraction 1 gave IV, which crystallized from methanol (400 mg), m.p. and m.m.p.[3,13] 110° (Found: C, 85.0; H, 10.2. Calc. for $C_{26}H_{38}O$: C, 85.2; H, 10.4%); IR: 1680 (C=C−C=O) and 1590 (C=C, aromatic); UV: 295, 253; PMR: δ 8.0 (*dd*, 1H, C_4-H, J = 8 Hz, *o*-coupled and J = 2 Hz, *m*-coupled), 7.3 (complex *m*, 3H, C_1-H, C_2-H and C_3-H), 0.8 (3H, $C_{13}-CH_3$), 1.0 and 0.96 (methyl protons).

Fraction 2 gave V, which crystallized from methanol (700 mg), m.p. and m.m.p.[14] 128° (Found: C, 84.6; H, 10.9. Calc for $C_{27}H_{42}O$: C, 84.8; H, 11.1%); IR: 3120 (C=C−H), 1670 (−C=C−C=C−C=O) and 1625 cm^{-1} (C=C); UV: 316.4; PMR: 6.6 (*dd*, 1H, C_4-H, $J_{C4-H,\,C3-H}$ = 6 Hz; $J_{C4-H,C2-H}$ = 2 Hz), 5.96 (*m*, 2H, C_2-H and C_3H), 2.3 (complex *m*, 2H, C_7-H_2), 1.0, 0.95, 0.85 and 0.7 (methyl protons).

Fraction 3 gave VI. It crystallized from methanol (200 mg), m.p. and m.m.p.[15] 168° (Found: C, 80.8; H, 10.8. Calc for $C_{27}H_{44}O_2$: C, 81.0; H, 11.0%); IR: 1710 (C=O); PMR: 2.3 (*m*, 7H, C_2-H_2, C_4-H_2, C_5-H and C_7-H_2), 1.2, 0.9, 0.8 and 0.66 (methyl protons).

II[15] (2 g) under similar reaction conditions and subsequent work-up followed by elution (column chromatography) with 40:1, 35:1, 20:1, 15:1 and 6:1 light petroleum-ether afforded five fractions respectively. Fraction 1 gave IV (350 mg). Fraction 2 gave V (700 mg). Fraction 3 gave VII which crystallized from methanol (60 mg), m.p. and m.m.p.[15] 109° (Found: C, 78.6; H, 10.3. Calc for $C_{29}H_{46}O_3$: C, 78.7; H, 10.4%); IR: 1740 (CH_3COO), 1690 (C=C−C=O), 1630 (C=C) and 1230 (acetate); PMR: 5.91 (*s*, 1H, C_4-vinylic H), 5.2 (complex *m*, 1H, $C_3-\alpha H$, axial, $W_{\frac{1}{2}}=16$ Hz), 2.0 (*s*, 3H, CH_3COO), 1.0, 0.91, 0.81 and 0.7 (methyl protons).

Fraction 4 gave VIII. It crystallized from methanol (100 mg), m.p. and m.m.p.[16] 127° (Found: C, 78.3; H, 10.7. Calc for $C_{29}H_{48}O_3$: C, 78.4; H, 10.8%); IR: 1735 (CH_3COO), 1710 (C=O), 1235 (acetate) and 1030 (C−O); PMR: 4.55 (*br*, 1H, $C_3-\alpha H$, axial, $W_{\frac{1}{2}}=16$ Hz), 1.96 (*s*, 3H, CH_3COO), 0.93, 0.83, 0.7 and 0.68 (methyl protons). Fraction 5 gave VI (800 mg).

III (2 g) under similar reaction conditions and usual work-up followed by column chromatography afforded the known IV (350 mg), and V (650 mg) and VI (50 mg). Compound (IX) was also isolated, which crystallized from methanol (100 mg), m.p. 134° (Found: C, 78.7; H, 10.4. $C_{30}H_{48}O_3$ requires C, 78.9; H, 10.6%); IR: 1735 ($-CH_3-CH_2-COO$), 1680 (C=C−C=O), 1630 (C=C), and 1180 (propionate); PMR: 5.93 (*s*, 1H, C_4-vinylic H), 5.23 (*m*, 1H, $C_3-\alpha H$, axial, $W_{\frac{1}{2}}=16$ Hz), 2.3 (*q*, 2H, CH_3CH_2COO, $J=7$ Hz), 1.23, 1.11, 1.0, 0.91, 0.81 and 0.7 (methyl protons).

Also isolated was compound (X), which crystallized from methanol (300 mg), m.p. 108° (Found: C, 78.4; H, 10.8. $C_{30}H_{50}O_3$ requires C, 78.6; H, 11.0%); IR: 1730 (CH_3CH_2COO), 1705 (C=O) and 1185 (propionate); PMR: 4.58 (*mc*, 1H, $C_3-\alpha H$, axial, $W_{\frac{1}{2}}=18$ Hz), 2.3 (*q*, 2H, CH_3CH_2COO, $J=7$ Hz), 1.2, 1.08, 0.9, 0.83, 0.75 and 0.65 (methyl protons).

One of us (SZA) is grateful to the CSIR, New Delhi for the award of a senior research fellowship.

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Syntheses of Agehoustins-A & B

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Agehoustins-A and B formulated as 5,6,7,8,2',3',4',5'-octamethoxyflavone (I) and 5,6,7,2',3',4',5'-heptamethoxyflavone (II) respectively, have been synthesised by the cyclodehydrogenations of the corresponding 2'-hydroxy-3',4',5',6',2,3,4,5-octamethoxychalkone (III) and 2'-hydroxy-4',5',6',2,3,4,5-heptamethxoychalkone (IV).

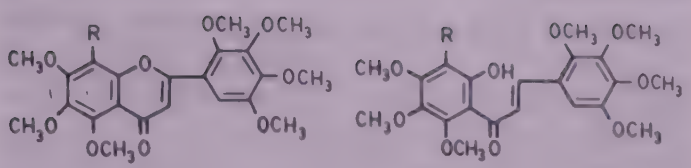
The two new polymethoxyflavonoid pigments, agehoustins-A and B isolated from *Ageratum houstonianum* by Quijano *et al.*[1] were found to have a very rare 2',3',4',5'-tetraoxygenation pattern in their side phenyl rings. On the basis of chemical and spectral data, agehoustins-A and B were assigned the structures as 5,6,7,8,2',3',4',5'-octamethoxyflavone (I) and 5,6,7,2',3',4',5'-heptamethoxyflavone (II), respectively. This note reports the syntheses of agehoustins-A and B.

Recently Linuma *et al.*[2] synthesised agehoustins-A and B, respectively by the cyclisation of 2'-hydroxy-3',4',5',6',2,3,4,5-octamethoxychalcone (III) and 2'-hydroxy-4',5',6',2,3,4,5-heptamethoxychalcone (IV) followed by the oxidation of the resulting flavones with DDQ.

Agehoustin-A has now been synthesised using III, which in turn was obtained by the condensation of 2-hydroxy-3,4,5,6-tetramethoxyacetophenone[3] with 2,3,4,5-tetramethoxybenzaldehyde[4] (V). Similarly agehoustin-B has been synthesised using IV, which was prepared by the condensation of 2-hydroxy-4,5,6-trimethoxyacetophenone[5] with 2,3,4,5-tetramethoxybenzaldehyde[4] (V).

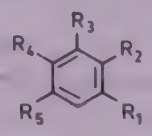
Cyclodehydrogenation of III and IV with selenium dioxide in isoamyl alcohol gave I and II, respectively. The analytical and spectral data of I and II agreed with those reported for agehoustins-A and B respectively.

Further Linuma *et al.*[2] prepared 2,3,4,5-tetramethoxybenzaldehyde (V) by a cumbersome procedure. During the course of present work V has now been prepared by a modified method involving the oxidation of 2,3,4-trimethoxybenzaldehyde using performic acid[6] followed by methylation of the resulting 1-hydroxy-2,3,4-trimethoxybenzene (VI).



(I) R = OCH_3
(II) R = H

(III) R = OCH_3
(IV) R = H



(V) R_1 = CHO ; $R_2 = R_3 = R_4 = R_5 = OCH_3$
(VI) R_1 = H ; R_2 = OH ; $R_3 = R_4 = R_5 = OCH_3$
(VII) $R_1 = R_2 = R_3 = R_4 = R_5 = OCH_3$

Formylation of the methylation product (VII) of VI gave the required aldehyde (V).

2'-Hydroxy-3',4',5',6',2,3,4,5-octamethoxychalkone (III)

A mixture of 2-hydroxy-3,4,5,6-tetramethoxyacetophenone[3] (0.5 g) and 2,3,4,5-tetramethoxybenzaldehyde (V, 0.8 g) in ethanol (10 ml) was treated with aq. potassium hydroxide (1.5 g in 10 ml) and then kept at room temperature for 48 hr. The usual work-up provided III, which crystallised from methanol as yellowish-orange needles (0.42 g), m.p. 48-49°, $C_{23}H_{28}O_{10}$. It gave brown colouration with ethanolic ferric chloride; PMR (δ, $CDCl_3$): 3.78 (3H, *s*, $-OCH_3$), 3.82 (3H, *s*, $-OCH_3$), 3.86 (6H, *s*, $2\times -OCH_3$), 3.94 (6H, *s*, $2\times -OCH_3$), 3.99 (3H, *s*, $-OCH_3$), 4.08 (3H, *s*, $-OCH_3$), 7.28 (1H, *s*, C_6-H), 7.76 (1H, *d*, $J = 15$ Hz, $C-\alpha-H$), 7.84 (1H, *d*, $J = 15$ Hz, $C-\beta-H$), 13.82 (1H, *s*, C-2'-OH).

5,6,7,8,2',3',4',5'-octamethoxyflavone (agehoustin-A, I)

A mixture of III (0.4 g), selenium dioxide (0.2 g) and isoamyl alcohol (15 ml) was refluxed in an oil-bath for 72 hr. Usual work-up afforded I which crystallised from chloroform-pet. ether as colourless needles (0.3 g), m.p. 116-17°, $C_{23}H_{26}O_{10}$. It did not give any colouration with ethanolic ferric chloride; PMR (δ, $CDCl_3$): 3.86 (3H, *s*, $-OCH_3$), 3.88 (3H, *s*, $-OCH_3$), 3.92 (12H, *s*, $4\times -OCH_3$), 3.99 (3H, *s*, $-OCH_3$), 4.05 (3H, *s*, $-OCH_3$), 6.66 (1H, *s*, C-3-H), 7.11 (1H, *s*, C-6'-H).

2'-Hydroxy-4',5',6',2,3,4,5-heptamethoxychalkone (IV)

A solution of 2-hydroxy-4,5,6-trimethoxyacetophenone[4] (1 g) in ethanol (10 ml) was treated with

2,3,4,5-tetramethoxybenzaldehyde (V, 1.2 g) and aq. potassium hydroxide (10%, 10 ml). The reaction mixture was stirred for 2 hr and left at room temperature for 72 hr. Usual work-up gave IV which crystallised from ethanol as orange-yellow needles (1.5 g), m.p. 101°, $C_{22}H_{26}O_9$; IR(KBr): 1620 (>C=O) cm^{-1}; UV(MeOH): 256 (sh), 370 nm; PMR(δ, $CDCl_3$): 3.77 (3H, *s*, $-OCH_3$), 3.85 (9H, *bs*, $3\times -OCH_3$), 3.90 (9H, *bs*, $3\times -OCH_3$), 6.27 (1H, *s*, C-3′-H), 6.88 (1H, *s*, C-6-H), 7.8 (1H, *d*, $J=16$ Hz, C-α-H), 8.07 (1H, *d*, $J=16$ Hz, C-β-H), 13.8 (1H, *s*, C-2′-OH).

5,6,7,2′,3′,4′,5′-Heptamethoxyflavone (agehoustin-B, II)

A mixture of IV (1 g), selenium dioxide (0.4 g) in isoamyl alcohol (15 ml) was refluxed for 72 hr. Usual work-up gave II which crystallised from chloroform-pet. ether as colourless needles (0.35 g), m.p. 98-100°, $C_{22}H_{24}O_9$. It did not give any colouration with ethanolic ferric chloride but gave pinkish red colouration with Mg/HCl; IR(KBr): 1635 (>C=O) cm^{-1}; UV(MeOH): 237 (sh), 265 (sh), 312 nm; PMR (δ, $CDCl_3$): 3.89 (3H, *s*, $1\times -OCH_3$), 3.94 (9H, *s*, $3\times -OCH_3$), 4.00 (9H, *s*, $3\times -OCH_3$), 6.78 (1H, *s*, C-3-H), 6.81 (1H, *s*, C-8-H), 6.99 (1H, *s*, C-6′-H).

The authors wish to thank the CSIR and UGC, New Delhi for financial support.

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Synthesis of 5,4′-Dihydroxy-3,7,8,2′-tetramethoxyflavone, a New Pigment from *Notholaena affinis*

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5,4′-Dihydroxy-3,7,8,2′-tetramethoxyflavone (I), a new pigment isolated from *Notholaena affinis* [*Can J Chem*, **57** (1979) 1901] has been synthesised by two unambiguous methods thereby providing unequivocal support for its structure.

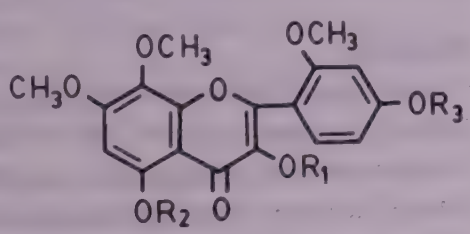
A new polyoxygenated flavone isolated from *Notholaena affinis* by Jay *et al.*[1] was formulated as 5,4′-dihydroxy-3,7,8,2′-tetramethoxyflavone (I) on the basis of its spectral data. However, no synthetic proof was provided in support of the formulation (I). In this note is described the synthesis of I by two methods thereby confirming its proposed structure.

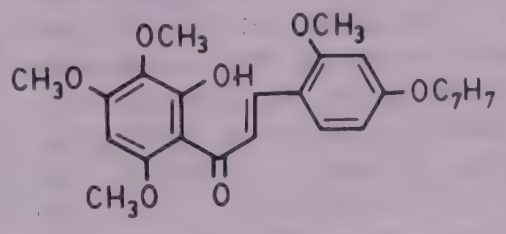
In the first approach the starting 2′-hydroxy-3′,4′,6′,2-tetramethoxy-4-benzyloxychalkone (II), prepared by the condensation of 2-hydroxy-3,4,6-trimethoxyacetophenone[2] and 2-methoxy-4-benzyloxybenzaldehyde[3] on Algar-Flynn - Oyamada oxidation[4,5] furnished 4′-benzyloxy-3-hydroxy-5,7,8,2′-tetramethoxyflavone (III). Methylation of III led to 4′-benzyloxy-3,5,7,8,2′-pentamethoxy flavone (IV), which on selective demethylation as well as debenzylation afforded I.

In the second approach 2-(4′-benzyloxy-2′-methoxy) benzoyloxy-3,4-6-trimethoxyacetophenone (V), on Baker-Venkataraman migration[6,7] yielded 2-hydroxy-3,4,6,2′-tetramethoxy-4′-benzyloxydibenzoylmethane (VI). Oxidation[8] of VI using performic acid[9] brought about hydroxylation of reactive methylene group as well as cycledehydration to give III. Conversion of III into I is also achieved by the first approach. The properties of the synthetic I were found to be identical with those reported for the natural sample.

2′-Hydroxy-3′,4′,6′,2-tetramethoxy-4-benzyloxychalkone (II)

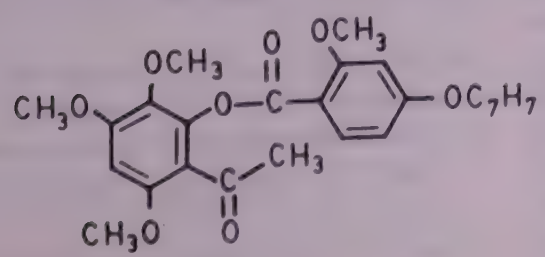
2-Hydroxy-3,4,6-trimethoxyacetophenone[2] (2g) in ethanol (15 ml) was treated with 2-methoxy-4-benzyloxybenzaldehyde[3] (2.5 g) and aq. sodium hydroxide (20 ml, 10%), and the reaction mixture left at room temperature for 72 hr. Usual work-up afforded II ($C_{26}H_{26}O_7$) which crystallised from ethanol to give yellow orange needles (2.5 g), m.p. 142°; PMR ($CDCl_3$): δ3.78 (6H, *s*, $2\times -OCH_3$), 3.85 (6H, *s*, $2\times -OCH_3$), 5.03 (2H, *s*, $-OCH_2C_6H_5$), 5.94 (1H, *s*, $C_5'-H$), 6.5-6.63 (2H, *m*, C_3-H and C_5-H), 7.36 (5H, *bs*, $-OCH_2C_6H_5$), 7.47 (1H, *d*, $J = 9$ Hz, C_6-H), 7.81 (1H, *d*, $J = 16$ Hz, $C_\alpha-H$), 8.10 (1H, *d*, $J = 16$ Hz, $C_\beta-H$), 14.08 (1H, *s*, C_2-OH).



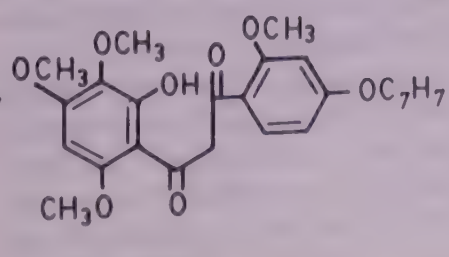


(II)

(I) $R_1 = CH_3$; $R_2 = R_3 = H$
(III) $R_1 = H$; $R_2 = CH_3$; $R_3 = C_7H_7$
(IV) $R_1 = R_2 = CH_3$; $R_3 = C_7H_7$
(VII) $R_1 = CH_3$; $R_2 = R_3 = COCH_3$



(V)



(VI)

4'-Benzyloxy-3,5,7,8,2'-Pentamethoxy-flavone (IV)

AFO oxidation[4,5] of II (0.6 g) with hydrogen peroxide and alkali afforded III ($C_{26}H_{24}O_8$) which crystallised from ethyl acetate-petroleum ether as colourless needles (0.5 g), m.p. 181-82°. III developed an olive-green colouration with ethanolic ferric chloride; PMR ($CDCl_3$):δ3.72 (3H, *s*, $-OCH_3$), 3.76 (3H, *s*, $-OCH_3$), 3.90 (6H, *s*, 2 × $-OCH_3$), 5.08 (2H, *s*, $-OCH_2C_6H_5$), 6.13 (1H, *s*, C_6-H), 6.6 - 6.7 (2H, *m*, $C_{3'}-H$ and $C_{5'}-H$), 7.41(6H, *bs*, $C_{6'}-H$ and $-OCH_2C_6H_5$).

Methylation of III (0.45 g) furnished IV ($C_{27}H_{26}O_8$) as colourless needles (0.4 g) from chloroform-pet. ether, m.p. 131-33°; PMR ($CDCl_3$):δ 3.71 (6H, *s*, 2 × $-OCH_3$), 3.76 (3H, *s*, $-OCH_3$), 3.82 (3H, *s*, $-OCH_3$), 3.86 (3H, *s*, $-OCH_3$), 5.0(2H, *s*, $-OCH_2C_6H_5$), 6.27 (1H, *s*, C_6-H), 6.47-6.54(2H, *m*, $C_{3'}-H$ and $C_{5'}-H$), 7.24(6H, *bs*, $C_{6'}-H$ and $-OCH_2C_6H_5$).

5,4'-Dihydroxy-3,7,8,2'-tetramethoxyflavene (I) and its di-O-acetyl derivative (VII)

A mixture containing IV (0.35 g), dry acetonitrile (10 ml) and anhydrous $AlCl_3$ was refluxed for 4 hr. Usual work-up gave I which crystallised from ethyl acetate-pet. ether as yellow needles (0.15 g), m.p. 218° (d), $C_{19}H_{18}O_8$; IR (KBr): 1640 (>C=O) cm^{-1}; UV (MeOH): 254 (sh), 268 (sh), 354 nm; + $AlCl_3$: 272, 346, 412 nm; + $AlCl_3$ + HCl: 272, 346, 414 nm; + NaOMe : 264, 285 (sh), 386 nm; + NaOAc : 254 (sh), 268, 380 nm; + H_3BO_3 : 254 (sh), 264, 354 nm; PMR ($CDCl_3$) : δ3.75 (3H, *s*, $-OCH_3$), 3.84 (3H, *s*, $-OCH_3$), 3.89 (3H, *s*, $-OCH_3$), 3.94 (3H, *s*, $-OCH_3$), 6.44-6.57 (3H, *m*, $C_{3'}-H$, $C_{5'}-H$ and C_6-H). 7.33 (1H, *m*, $C_{6'}-H$).

Di-O-acetyl derivative (VII) of I was prepared as usual (Ac_2O/Py, 1 hr heating at 90-100°) and crystallised from ethyl acetate-pet. ether, as colourless needless, m.p. 232-33°, $C_{23}H_{22}O_{10}$; PMR ($CDCl_3$): δ2.34 (3H, *s*, $-OCOCH_3$), 2.46 (3H, *s*, $-OCOCH_3$), 3.81 (3H, *s*, $-OCH_3$), 3.85 (6H, *s*, 2 × $-OCH_3$), 3.96 (3H, *s*, $-OCH_3$), 6.83-7.00 (3H, *m*, C_6-H, $C_{3'}-H$ and $C_{5'}-H$), 7.21 (1H, *m*, $C_{6'}-H$)

2-(4'-Benzyloxy-2'-methoxy)benzoloxy-3,4,6-trimethoxy acetophenone (V) and its migration to 2-hydroxy-3,4,6,2'-tetramethoxy-4'-benzyloxydibenzoylmethane (VI)

2-Hydroxy-3,4,6-trimethoxyacetophenene (1g) and 2-methoxy-4-benzyloxybenzoyl chloride (2 g) in dry pyridine (20 ml) were heated at 50-60° for 1 hr. Usual work-up afforded the ester (V) ($C_{26}H_{26}O_8$) which crystallised from ethyl acetate-pet. ether as colourless needles (1.4 g), m.p. 145°; PMR($CDCl_3$): δ2.5 (3H, *s*, $-COCH_3$), 3.82 (3H, *s*, $-OCH_3$), 3.90 (6H, *s*, 2 × $-OCH_3$), 3.95, (3H, *s*, $-OCH_3$), 5.16 (2H, *s*, $-OCH_2C_6H_5$), 6.46 (1H, *s*, C_5-H), 6.61-6.69 (2H, *m*, $C_{3'}-H$ and $C_{5'}-H$), 7.43 (5H, *bs*, $-OCH_2C_6H_5$), 8.0-8.09 (1H, *d*, J = 9 Hz, $C_{6'}-H$).

V (1.3 g) and powdered potassium hydroxide (2g) in dry pyridine (25 ml) when heated at 45-50° for 30 min and the reaction mixture left at room temperature for 2 hr gave VI ($C_{26}H_{26}O_8$) which crystallised from methanol as yellow needles (0.78 g), m.p. 196-98°; PMR ($CDCl_3$ + 1 drop of TFA): δ3.91 (6H, *s*, 2× $-OCH_3$), 4.03 (3H, *s*, $-OCH_3$), 4.1 (3H, *s*, $-OCH_3$), 5.2 (2H, *s*, $-OCH_2C_6H_5$), 6.56 (1H, *s*, C_5-H), 6.65-6.75 (2H, *m*, $C_{3'}-H$ and $C_{5'}-H$), 7.37 (5H, *bs*, $-OCH_2C_6H_5$), 7.74 (1H, *s*, $-C(=O)-CH=C(-OH)-$), 8.1-8.19 (1H, *d*, J = 9 Hz, $C_{6'}-H$).

4'-Benzyloxy-3-hydroxy-5,7,8,2'-tetramethoxyflavone (III)

Performic acid (8 ml) and VI (0.5 g) in chloroform (25 ml) were refluxed on a boiling water-bath for 3 hr. Usual work-up afforded III which crystallised from ethyl acetate-pet. ether as colourless needles (0.180 g), m.p. and m.m.p. 181-82°.

Two of the authors (GC and AJ) thank the CSIR, New Delhi for financial support.

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Further Investigation on [3,3]-Sigmatropic Rearrangement of Allyl Ethers of 4-Hydroxycoumarin†

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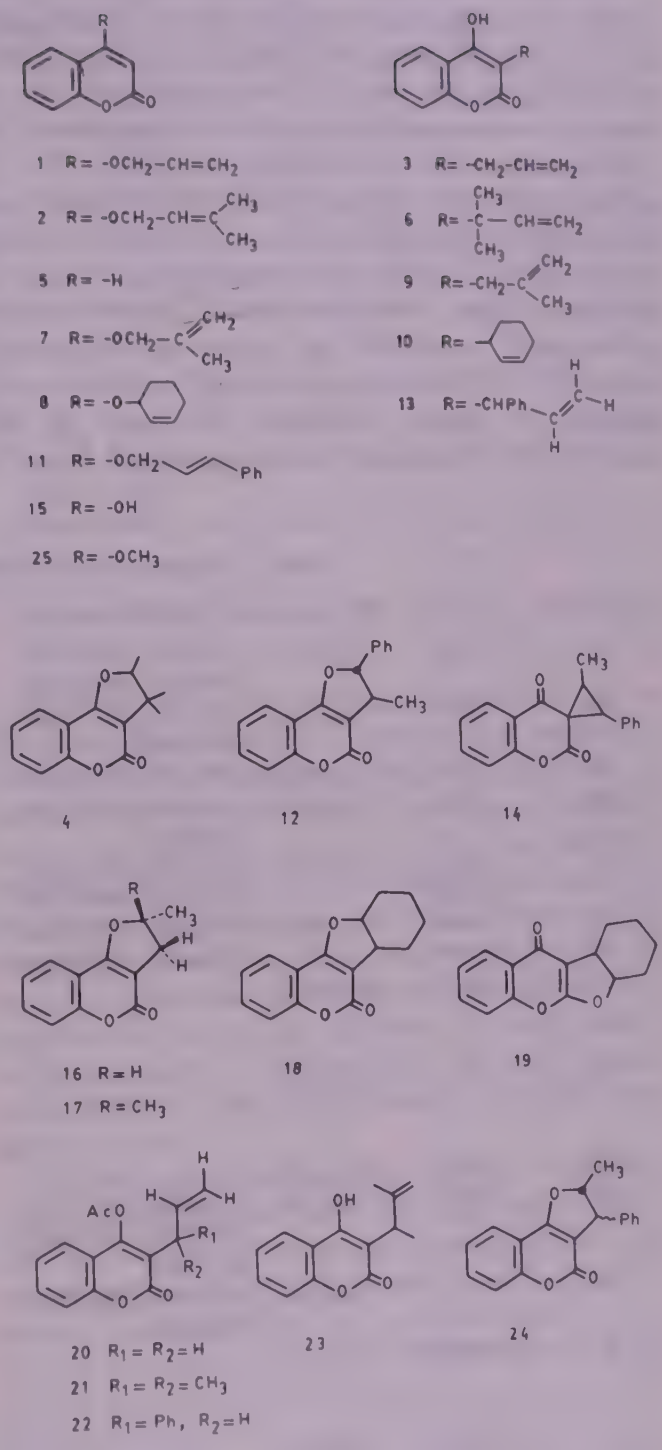
Pyrolytic [3, 3]-sigmatropic rearrangements of 4-(2-methylalloyloxy) coumarin (**7**), 4-(cyclohex-2-enyloxy) coumarin (**8**) and 4-cinnamyloxycoumarin (**11**) afford 4-hydroxy-3-(2-methylallyl) coumarin (**9**), 3-(cyclohex-2-enyl)-4-hydroxycoumarin (**10**) and *trans*-2, 3-dihydro-3-methyl-2-phenylfuro [3,2-*c*] [1] benzopyran-2(*H*)-one (**12**), respectively. Refluxing of allyloxycoumarins **1**, **2**, **7** and **11** in high boiling solvents (N, N-dimethylaniline and diphenyl oxide) furnishes the dihydrofuran derviatives while **8** gives no such cyclized product but **10**. The hydroxyallylcoumarins **3** and **9** also undergo facile cyclization to dihydrofuran derivatives in dil. mineral acids at room temperature whereas **10** and **13** require cold conc. sulphuric acid. Refluxing of **2** and **11** with acetic anhydride and fused sodium acetate yields 3-allyl derivatives (**21** and **22**) of 4-acetoxycoumarin. Treatment of **21** with potassium carbonate in methanol at room temperature gives a rearranged hydrolysis product (**23**) whereas **22** under similar conditions undergoes usual hydrolysis to give **13**. Carbon-13 NMR signal assignments of the allyl ethers of 4-hydroxycoumarin and their rearrangement products are also reported along with their preliminary antimicrobial activity.

4-Hydroxycoumarin and its derivatives are biologically active compounds[1]. Several workers have studied[2-8] the sigmatropic rearrangement of their allyl ethers. Further, 3-allylcoumarin and two 3-(1, 1-dimethylallyl) coumarins have been prepared recently by this rearrangement[6,8]. The reactivity of 4-allyloxycoumarin[2,4] (**1**), 4-(3, 3-dimethylalloxy) coumarin[4] (**2**) and 4-cinnamyloxycoumarin[7] (**11**) towards thermal rearrangement was, however, somewhat different from that of the corresponding allyl ethers of 3-hydroxycoumarin reported recently by us[9]. We were thus interested in carrying out further investigation on [3, 3]-sigmatropic rearrangement of allyl ethers of 4-hydroxycoumarin. We report here the results of this study and also the results of our preliminary observation on antimicrobial activities of these compounds.

Like 4-allyloxycoumarin[4] (**1**), pyrolysis of 4-(2-methylallyloxy) coumarin (**7**) and 4-(cyclohex-2-enyloxy) coumarin (**8**) under reduced pressure led to 4-hydroxy-3-(2-methylallyl) coumarin (**9**) and 3-(cyclohex-2-enyl)-4-hydroxycoumarin (**10**), respectively as the sole products (yield 55-60%). However, 4-cinnamyloxycoumarin[7] (**11**) gave exclusively the cyclized abnormal rearrangement product *trans*-2, 3-dihydro-3-methyl-2-phenylfuro [3, 2-*c*] [1] benzopyran-2(*H*)-one (**12**) (yield ~75%). Similar abnormal rearrangement was also reported during Claisen rearrangement of 7-cinnamyloxycoumarins[10] and 4-cinnamyloxycoumarins[7] in refluxing N, N-dimethylaniline. Pyrolysis of 4-hydroxy-3-(1-



†Part of the Ph.D. Thesis of A K Mukhopadhyay, University of Calcutta, 1980.

phenylallyl) coumarin (**13**), derived by a different sequence of reactions (*vide infra*), also furnished **12**. Compound **12** is thus probably derived from the cyclopropyl intermediate **14** formed from the usual Claisen rearrangement product **13** via a subsequent ($\pi^2S+\pi^2S+\sigma^2S$)-type cycloaddition reaction involving allylic double bond, 3, 4-double bond of the coumarin nucleus and phenolic O – H sigma bond. The transformation **14**→**12** possibly involves a [1, 3]-sigmatropic shift of the more labile cyclopropane bond (between C-3 of coumarin nucleus and carbon bearing phenyl group in **14**) where migration terminus is carbonyl oxygen. The allyl ethers **7**, **8** and **11** were conveniently prepared by refluxing 4-hydroxycoumarin[11] (**15**) with appropriate allyl bromides in the presence of anhyd. potassium carbonate in dry acetone. The structures of the compounds **7**, **8** and **11** were established by their elemental analyses and spectra data (Tables 1 and 2).

Unlike the 4-allyl derivatives of 3-hydroxycoumarin reported earlier[9], the 3-allyl derivatives (**3** and **9**) of 4-hydroxycoumarin underwent smooth cyclization to dihydrofuro derivatives (**16** and **17**, respectively) when stirred in dil. (2*N*) mineral acids (HCl or H_2SO_4) at room temperature 3-(Cyclohex-2-enyl)-4-hydroxycoumarin (**10**) remained unchanged under similar conditions but afforded a mixture of 2, 3-cyclohexo-2, 3-dihydrofuro [3,2-*c*] [1] benzopyran-2(*H*)-one (**18**) and 2, 3-cyclohexo-2, 3-dihydrofuro [2, 3-*b*] [1] benzopyran-4(*H*)-one (**19**) on treatment with cold conc. H_2SO_4.

Refluxing of the allyl ethers **1**[4], **2**[4], **7** and **11** in high boiling solvents such as diphenyl oxide, N, N-dimethylaniline and subsequent work-up following an

Table 1—Physical Characteristics of the Coumarins Reported

Compound‡	m.p. (°C)	Mol. formula	UV (EtOH) nm (log ε)	PMR (δ_{TMS}, $CDCl_3$, 80 MHz)
7	102	$C_{13}H_{12}O_3$	214 (4.36), 266 (4.02), 276 (4.01), 303 (3.82)	1.90 (*s*, 3H), 4.60 (*s*, 2H), 5.15 (*m*, 2H), 5.70 (*s*, 1H), 7.1-7.7 (*m*, 3H), 7.85 (*dd*, *J* = 8.0, 2.0 Hz, 1H)
8	128	$C_{15}H_{14}O_3$	267 (4.07), 278 (4.05), 303 (3.87)	1.68-2.15 (*m*, 6H), 4.89 (*m*, 1H), 5.65 (*s*, 1H), 5.95 (*m*, 2H), 7.07-7.58 (*m*, 3H), 7.77 (*m*, 1H)
9	110	$C_{13}H_{12}O_3$	240 (3.89), 312 (4.08)	1.85 (*s*, 3H), 3.48 (*s*, 2H), 5.07 (*m*, 2H), 7.1-7.65 (*m*, 3H), 7.80 (*m*, 1H)
10	109	$C_{15}H_{14}O_3$	211 (4.48), 236 (3.93), 314 (4.11)	1.67-2.28 (*m*, 6H), 3.83 (*m*, 1H), 6.17 (*m*, 2H), 7.19-7.72 (*m*, 3H), 7.68 (*s*, 1H, D_2O exchangeable), 7.77 (*m*, 1H)
11	162 (163-64)[7]	$C_{18}H_{14}O_3$	211 (4.56), 255 (4.41), 293 (3.78), 303 (3.79)	4.86 (*d*, *J* = 5.6 Hz, 2H), 5.75 (*s*, 1H), 6.42 (*dt*, *J* = 16.0, 5.6 Hz, 1H), 6.84 (*d*, *J* = 16.0 Hz, 1H), 7.0-7.7 (*m*, 8H), 7.90 (*dd*, *J* = 8.0, 1.5 Hz, 1H)
12	148-49 (149-50)[7]	$C_{18}H_{14}O_3$	278 (3.84), 289 (3.98), 313 (4.01), 327 (3.87)	0.91 (*d*, *J* = 7.1 Hz, 3H), 3.83 (*dq*, *J* = 9.7, 7.1 Hz, 1H), 6.13 (*d*, J = 9.7 Hz, 1H), 7.0-7.6 (*m*, 8H), 7.77 (*m*, 1H)
13	132	$C_{18}H_{14}O_3$	—	5.22 (*dt*, *J* = 16.8, 1.6 Hz, 1H), 5.31 (*m*, 1H), 5.50 (*dt*, *J* = 10.4, 1.6 Hz, 1H), 6.49 (*ddd*, *J* = 16.8, 10.4, 5.6 Hz, 1H), 7.19-7.66 (*m*, 8H), 7.80 (*dd*, *J* = 8.3, 1.4 Hz, 1H)
16	94	$C_{12}H_{10}O_3$	—	1.58 (*d*, *J* = 6.2 Hz, 3H), 2.78 (*dd*, *J* = 14.8, 7.3 Hz, 1H), 3.33 (*dd*, *J* = 14.8, 9.8 Hz, 1H), 5.30 (*m*, 1H), 7.1-7.6 (*m*, 3H), 7.63 (*dd*, *J* = 8.0, 2.0 Hz, 1H)
17	115	$C_{13}H_{12}O_3$	—	1.62 (*s*, 6H), 2.98 (*s*, 2H), 7.14-7.75 (*m*, 4H)
18	140-41	$C_{15}H_{14}O_3$	218 (4.06), 272 (3.89), 283 (3.99), 295 (3.85), 306 (3.98)	1.3-2.3 (*m*, 6H), 3.23 (br *s*, 1H), 4.86 (br *s*, 1H), 7.1-7.6 (*m*, 3H), 7.76 (*dd*, *J* = 8.8, 1.6 Hz, 1H)
19	107-8	$C_{15}H_{14}O_3$	229 (4.05), 278 (4.01), 288 (3.99)	1.3-2.3 (*m*, 6H), 3.45 (br *s*, 1H), 4.92 (br *s*, 1H), 7.2-7.7 (*m*, 3H), 8.27 (*dd*, *J* = 8.0, 1.6 Hz, 1H)
20	Amorphous	$C_{14}H_{12}O_4$	—	2.48 (*s*, 3H), 3.29 (*dt*, *J* = 6.4, 1.6 Hz, 2H), 5.10 (*dq*, *J* = 9.6, 1.6 Hz, 1H), 5.17 (*dq*, *J* = 16.8, 1.6 Hz, 1H), 5.89 (*ddt*, *J* = 16.8, 9.6, 6.4 Hz, 1H), 7.21-7.48 (*m*, 3H), 7.59 (*dd*, *J* = 8.0, 2.4 Hz, 1H)
21	Amorphous	$C_{16}H_{16}O_4$	—	1.52 (*s*, 6H), 2.33 (*s*, 3H), 4.98 (*dd*, *J* = 10.4, 1.2 Hz, 1H), 5.02 (*dd*, *J* = 17.6, 1.2 Hz, 1H), 6.25 (*dd*, *J* = 17.6, 10.4 Hz, 1H), 7.21-7.61 (*m*, 4H)
22	126	$C_{20}H_{16}O_4$	—	2.23 (*s*, 3H), 5.04 (*dt*, *J* = 7.2, 1.6 Hz, 1H), 5.16 (*dt*, *J* = 10.4, 1.6 Hz, 1H), 5.22 (*dt*, *J* = 18.2, 1.6 Hz, 1H), 6.46 (*ddd*, *J* = 18.2, 10.4, 7.2 Hz, 1H), 7.15-7.85 (*m*, 9H)
23	116	$C_{14}H_{14}O_3$	—	1.34 (*d*, *J* = 7.2 Hz, 1H), 1.79 (*s*, 3H), 3.79 (br *q*, *J* = 7.2 Hz, 1H), 5.26 (*m*, 2H), 7.17-7.45 (*m*, 3H), 7.61 (*s*, 1H, D_2O exchangeable), 7.77 (br *d*, *J* = 8.2 Hz, 1H)
24	—	—	—	(*cis*-) 1.16 (*d*, *J* = 6.9 Hz, 3H), 4.19 (*d*, *J* = 6.1 Hz, 1H), 5.0 (*m*, 1H), 7.14-7.76 (*m*, 9H); (*trans*-) 1.63 (*d*, *J* = 7.0 Hz, 3H), 4.57 (*d*, *J* = 9.7 Hz, 1H), 5.39 (*m*, 1H), 7.14-7.76 (*m*, 9H)

‡Appropriate bands are present in the IR spectra of the compounds.

Table 2—Carbon-13 NMR Signals (δ) of the Coumarins **1-5**, **7-12**, **15-17**, **22** and **25**

	(1)[4]	(2)[4]	(3)[2]	(4)[4]	(7)[2]	(8)[2]	(9)[2]	(10)[2]	(11)[2]	(12)[2]	(15)[12]	(16)[2]	(17)[2]	(22)[2]	(25)[2]	(5)[13]
C-2	162.5	160.5	161.5	159.6	162.5	162.8	161.6	160.8	162.5	160.1	162.2	160.5	160.8	155.4	161.7	160.1
C-3	90.8	90.8	102.5	110.2	90.8	90.4	101.8	107.2	90.7	107.4	91.4	101.5	101.2	121.3	91.4	116.0
C-4	164.9	164.4	164.6	164.6	165.0	164.3	163.9	163.0	165.0	165.3	165.8	166.1	165.3	161.1	165.8	143.0
C-4a	115.5	115.9	115.9	112.6	115.6	115.9	115.6	115.9	115.5	116.8	116.1	112.4	112.8	116.0	115.1	118.3
C-5	122.8	123.0	123.1	122.4	122.8	123.0	122.9	122.7	123.0	122.7	123.3	122.4	122.6	122.8	122.6	127.5
C-6	123.7	123.6	123.9	123.3	123.7	123.5	123.8	123.6	123.6	123.8	123.7	123.5	123.6	124.1	123.9	123.9
C-7	132.1	132.1	131.7	131.7	132.2	132.0	131.8	131.5	132.1	132.3	132.4	131.9	132.0	131.8	132.5	131.3
C-8	116.5	116.6	116.6	116.6	116.5	116.3	116.3	116.1	116.5	116.8	116.3	116.6	116.8	116.6	116.3	116.1
C-8a	153.2	151.5	152.2	154.5	153.2	153.2	152.3	152.3	153.2	154.9	153.8	154.7	154.9	152.2	152.7	153.4
C-1′	69.6	66.1	27.9	43.6	72.5	72.3	32.5	32.9	69.6	39.0	—	33.7	39.6	46.0	56.8	
C-2′	130.5	117.6	134.3	92.3	138.3	134.1	143.6	134.7	128.3	90.9	—	83.9	92.7	135.9	—	—
C-3′	119.3	136.0	116.3	14.1	114.3	123.4	112.7	128.7	121.3	—	—	21.7	28.2	117.7	—	—
C-4′	—	25.9	—	25.4	19.1	24.7	21.8	25.0	—	14.7	—	—	28.2	—	—	—
C-5′	—	18.0	—	20.1	—	18.3	—	20.9	—	—	—	—	—	—	—	—
C-6′	—	—	—	—	—	27.5	—	27.9	—	—	—	—	—	—	—	—
C-1″	—	—	—	—	—	—	—	—	135.5	135.7	—	—	—	140.0	—	—
C-2″, 6″	—	—	—	—	—	—	—	—	126.5	126.2	—	—	—	127.6	—	—
C-3″, 5″	—	—	—	—	—	—	—	—	128.5	128.3	—	—	—	128.3	—	—
C-4″	—	—	—	—	—	—	—	—	135.0	128.2	—	—	—	126.6	—	—
$OCOCH_3$	—	—	—	—	—	—	—	—	—	—	—	—	—	166.7	—	—
														20.2		

[2]In $CDCl_3$; $\delta_{TMS} = \delta_{CDCl_3} + 76.9$ ppm.

earlier procedure[9] furnished the cyclized, rearrangement products **16**[2], **4**[4], **17** and **12**[7], respectively in 60-70% yield. However, under similar conditions 4-(cyclohex-2-enyloxy) coumarin (**8**) afforded **10** only but no cyclized product. This observation coupled with the inertness of **10** towards cyclization in dil. mineral acids as mentioned earlier suggests that the cyclohexane moiety in **10** exists in sterically unfavourable conformation to effect an analogous cyclization as above due to the steric involvement of cyclohexene moiety in **10** with oxygens on either side. Interestingly enough, the product **10** was less polar than the parent compound **8** on silica gel plate with chloroform as eluent and the hydroxy band in the IR spectrum of **10** taken in KBr appeared as a broad band around 3060 cm^{-1}.

Refluxing of 4-allyloxycoumarin[4] (**1**), 4-(3, 3-dimethylallyloxy) coumarin[4] (**2**) and 4-cinnamyloxy-coumarin (**11**) separately in acetic anhydride in the presence of fused sodium acetate yielded acetyl derivatives of the usual rearrangement products, viz. 4-acetoxy-3-allylcoumarin[6] (**20**), 4-acetoxy-3-(1, 1-dimethylallyl) coumarin (**21**) and 4-acetoxy-3-(1-phenylallyl) coumarin (**22**), respectively in about 75-95% yield. Treatment of **21** in methanol with potassium carbonate at room temperature unexpectedly afforded a further rearrangement product 3-(1, 2-dimethylallyl)-4-hydroxycoumarin (**23**) in almost quantitative yield. A plausible mechanism involves a $(\pi^2S+\pi^2S+\sigma^2S)$-type cycloaddition of incipient 3-(1, 1-dimethylallyl)-4-hydroxycoumarin (**6**) as in the thermal transformation of **11** to **12**, succeeded by another $(\pi^2S+\sigma^2S+\sigma^2S)$-type concerted reaction involving the carbonyl of the cyclopropanone so generated, a cyclopropane bond (between C-3 of coumarin nucleus and carbon bearing *gem*-dimethyl) and a C−H sigma bond of one of the *gem*-dimethyls. However, 4-acetoxy-3-(1-phenylallyl) coumarin (**22**) gave the usual hydrolysis product 4-hydroxy-3-(1-phenylallyl) coumarin (**13**) in about 75% yield by the action of potassium carbonate in methanol at room temperature. Coumarin **13** gave *cis*- and *trans*-2-methyl-3-phenyl-2, 3-dihydrofuro [3,2-*c*] [1] benzopyran-2(*H*)-ones (**24**) when treated with cold conc. sulphuric acid.

The CMR signal assignments of the allyl ethers of 4-hydroxycoumarin and their rearrangement products given in Table 2 were made using the spectra of model compounds 4-hydroxycoumarin[12] (**15**) and 4-methoxycoumarin (**25**) as well as of coumarin **5**[13] and also by consideration of substitution effects[14]. The allyloxy function at C-4 exhibited unusually strong shielding effects on C-3 (25.2-25.6 ppm in **1**, **2**, **7**, **8** and **11** relative to coumarin **5**. It was also noteworthy that C-4 underwent relatively small downfield shift (21.3-22.0 ppm) due to attachment with an ether function and that the oxygen substituents at C-4 caused an upfield shift of C-5 resonances by about 4.5-4.7 ppm again with respect to simple coumarin probably due to γ-effect of the oxygen substituent at C-4. It was further observed that O-allylation of 4-hydroxycoumarin did not alter the chemical shift for the carbons of the coumarin moiety which were also closely analogous to those in 4-methoxycoumarin (**25**).

Preliminary antimicrobial testing of the allyl ethers **1**, **2**, **7**, **8** and **11** and their rearrangement products **3**[4], **4**, **10**, **12**, **13**, **20** and **22** was carried out by conventional agar diffusion method against *Staphylococcus aureus*, *Bacillus subtilis* and *Escherichia coli*. Compounds **3**, **10**, **13**, **20** and **22** showed considerable activity against *S. aureus* and *B. subtilis* but **10** also had some activity against the gram negative bacteria *E. coli*. These five compounds were also active against the fungal strains *Trycophyton rubrun*, *Trycophyton tonsurans* and *Microsporium gypsum*.

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Wittig Reaction of 2-Hydroxy-4,6-dimethoxybenzophenone with α-Ethoxycarbonylbenzylidenetriphenylphosphorane: Unusual Formation of 4,6-Dimethoxy-2-phenylbenzofuran

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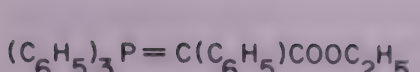
Formation of 4,6-dimethoxy-2-phenylbenzofuran (**3**), instead of the expected 5,7-dimethoxy-3,4-diphenylcoumarin is observed in the Wittig reaction of 2-hydroxy-4,6-dimethoxybenzophenone (**2**) with α-ethoxycarbonylbenzylidenetriphenylphosphorane (**1**).

3,4-Diphenylcoumarins[1] have been known for their marked antifertility activity. Phenylcoumarins[2] have been synthesised by a convenient route involving Wittig reaction. In an attempt to synthesise 3,4-diphenylcoumarins by the Wittig reaction of 2-hydroxy-4,6-dimethoxybenzophenone (**2**) with α-ethoxycarbonylbenzylidenetriphenylphosphorane (**1**), we have presently observed that the product is not the expected 5,7-dimethoxy-3,4-diphenylcoumarin (**4**), but 4,6-dimethoxy-2-phenylbenzofuran (**3**) as revealed by its ^{1}H and ^{13}C NMR, mass and IR spectral data. The identity of **3** has been further confirmed by direct comparison (m.p., m.m.p. and co-IR) with an authentic sample prepared by the condensation of 2-hydroxy-4,6-dimethoxybenzaldehyde with ethyl α-bromophenylacetate following the earlier known procedure[3] for such compounds.

At present it is not possible to suggest a pathway for the formation of **3** from **1** and **2**.

A typical experiment involved heating of a mixture of **1** (0.424 g, 1 mmol) and **2** (0.248 g, 1 mmol) at 250° for 8 hr. The resultant mixture was subjected to column chromatography over silica gel using pet ether



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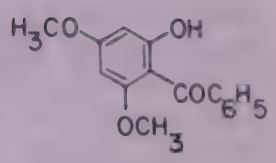

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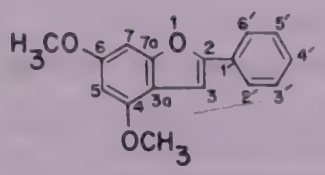

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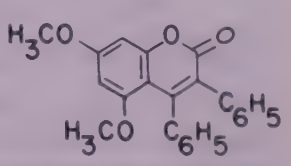

4

as an eluent. Compound **3** (yield 25%) obtained, was crystallised from benzene-pet ether as colourless needles, m.p. 70-71° (Found: C, 75.1; H, 5.6. $C_{16}H_{14}O_3$ requires C, 75.6; H, 5.5%); MS: *m/z* 254 (M^+); IR(KBr): 1600, 1100-1140; PMR($CDCl_3$): δ 3.85, 3.9 (each *s*, each 3H, 2 × OCH_3), 6.35 (*d*, *J* = 2 Hz, 1H, C_5-H), 6.7 (*d*, *J* = 2 Hz, 1H, C_7-H), 7.05 (*s*, 1H, C_3-H), 7.4 (*m*, 3H, $C_{3'}-H$, $C_{4'}-H$ and $C_{5'}-H$), 7.8 (*m*, 2H, $C_{2'}-H$ and $C_{6'}-H$); ^{13}C NMR ($CDCl_3$, decoupled): δ; 56.0 (2 × OCH_3), 154.60[a] (C−2), 99.24 (C−3), 154.30[a] (C−4), 94.74 (C−5), 159.02 (C−6), 89.80 (C−7), 157.60 (C−7a), 114.04 (C−3a), 131.68 (C−1'), 124.72 (C−2' and C−6'), 129.22[b] (C−3' and C−5'), 128.15[b] (C−4'). (a and b: assignments could be reversed). In the ^{13}C NMR (off resonance) spectrum of **3** the doublet at δ 99.24 has been assigned to C−3. This is in agreement with the ^{13}C NMR of 2-phenylbenzofurans[4].

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Synthesis of 2,6,10,14-Tetramethylpentadec-2-ene Using *p*-Toluenesulphonylacetic Esters†

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The title compound (VIII) has been prepared by successive alkylation of *p*-toluenesulphonylacetic acid esters (Ia,b) with dihydrocitronellyl bromide (II) and methylheptenyl iodide (IV) followed by decarbomethoxylation and desulphonation.

In our recent publications[1-4] we have described a new methodology for the synthesis of the title compound (VIII) and its isomer norphytene (IX) which are both naturally occurring hydrocarbons from which phytone, a useful intermediate for vitamin-E, has been obtained[5]. In this note we describe another approach for VIII using *p*-toluenesulphonylacetic acid methyl or *t*-butyl ester (Ia or Ib) as an active methylene compound for alkylation and for the addition of one carbon atom in our strategy ($C_1+C_{10}C_8$). The carbalkoxy group can be removed at a later stage, and for the removal of the sulphonyl group various reagents are available[6]. The reaction sequence is shown in Chart 1.

p-Toluenesulphonylacetic acid methyl ester[7] (Ia) was reacted with dihydrocitronellyl bromide (II) in the presence of sodium hydride in dimethylformamide[8] in equimolar proportions at 80-90° for 10-12 hr under nitrogen atmosphere until TLC showed the appearance of dialkylated product (TLC: solvent, benzene). Usual work-up gave a residue which was triturated with pet. ether whereby the starting ester (Ia) separated out (22%). The filtrate was column chromatographed over silicic acid. The pet. ether eluate gave the starting halide (II). Elution with 20% benzene in pet. ether gave the symmetrical dialkylated product (8.7%) and elution with 50% benzene in pet. ether furnished the monoalkylated product IIIa (R $=CH_3$) in 47% yield. The chromatographically pure IIIa showed IR (liquid film) bands at 1740 (COOMe), 1320 and 1145 cm^{-1} ($-SO_2-$), and PMR (CCl_4) signals at δ 0.84 (*d*, 9H $3\times -CH-CH_3$), 2.3 (*s*, 3H, Ar-CH_3), 3.6 (*s*, 3H, $-COOCH_3$), 3.8 (*m*, 1H, C_9-H), 7.2 (*dd*, 2H, Ar-*H*) and 7.8 (*dd*, 2H, Ar-*H*). The chromatographically pure dialkylated product showed IR bands at 1740 (ester $>C=O$) 1320 and 1150 cm^{-1} ($-SO_2-$) and PMR (CCl_4) signals at δ 3.6 (*s*, 3H, $-COOCH_3$) and δ 0.87 (*d*, 18H, $6\times CH_3$). The integration of ester methyl signal at δ 3.6 and the secondary methyl signal at 0.87 in the ratio 1:6 indicated the product to be dialkylated. In order to improve the yield of IIIa, the alkylation of

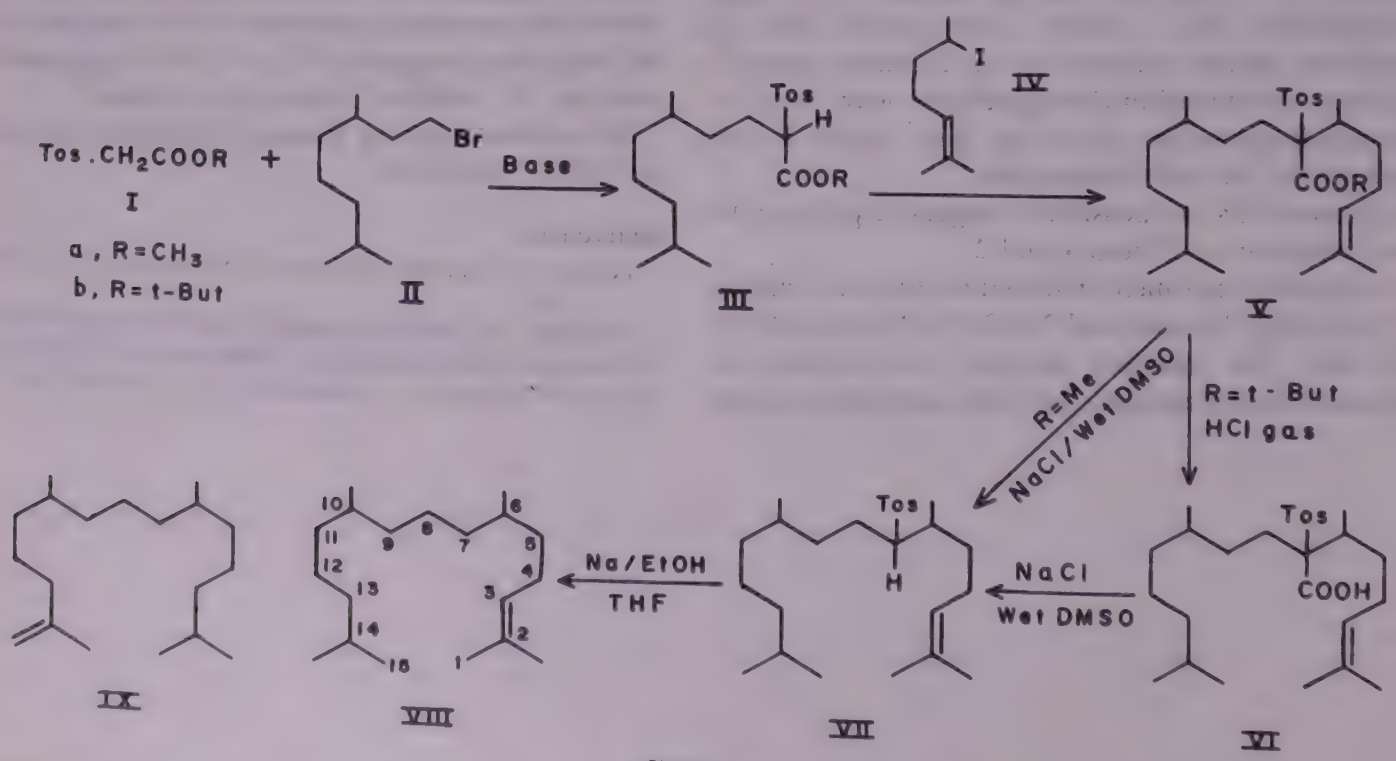

Chart 1

†NCL Communication No. 3940

Ia was carried out under PTC conditions using tetrabutylammonium iodide (20 mmol) and KOH (2 mol) in THF under nitrogen atmosphere at room temperature for 2 hr (reaction being monitored by TLC as above). However, work-up of the reaction mixture gave IIIa in a similar yield. Further alkylation of IIIa with methylheptenyl iodide (IV) in the presence of sodium hydride in dimethylformamide[8] under nitrogen atmosphere at 80-90° for 24 hr gave the dialkylated product Va ($R=CH_3$) which was isolated by silica gel column chromatography as performed above. However, the yield of V was only 20%. There was no improvement in the yield of Va under PTC conditions (*vide supra*). The chromatographically pure Va showed IR bands at 1720 ($>C=O$), 1320 and 1150 cm^{-1} ($-SO_2-$), and PMR (CCl_4) signals at δ 2.5 (*s*, 3H, Ar-CH_3), 3.6 (*s*, 3H, $COOCH_3$), 1.56, 1.63 [2*s*, 6H, $-CH=C(CH_3)_2$] and 5.0 (*m*, 1H, $>C=CH-$). In all the alkylations, dry solvents were used and we found that sometimes the carbomethoxy group was knocked out perhaps due to moisture. In order to avoid this and to see whether yields could be improved, we used *p*-toluenesulphonylacetic acid *t*-butyl ester (Ib) since *t*-butyl esters are stable in alkaline conditions. Further, one can use aq. sodium hydroxide solution under PTC conditions. Under PTC conditions using 50% aq. NaOH or KOH in tetrahydrofuran using tetrabutylammonium iodide, there was no improvement in the yields of IIIb and Vb.

The dialkylated product Va (3.5 mmol) on treatment with sodium chloride (10.25 mmol) and H_2O (8.33 mmol) in freshly distilled dimethylsulphoxide[9] (5 ml) at 150-60° for 5 hr gave VII (91%). In the case of Vb, the *t*-butyl group was removed by treating with dry HCl gas in methylene chloride to obtain the acid VI which was decarboxylated under the same conditions as above. The chromatographically pure VII showed no IR bands at 1740, but it showed bands at 1320 and 1145 cm^{-1} thus confirming the presence of *p*-toluenesulphonyl group. In the PMR (CCl_4) spectrum of VII, the aromatic methyl protons appeared at δ 2.5 (*s*, 3H), vinylic *gem*-dimethyl protons at 1.56 and 1.63 (2*s*, 6H), olefinic proton at 5.00 (*m*, 1H) and C_7-H at 3.8 (*m*, 1H). Various reagents are reported to knock out the sulphonyl group[6]. We could not get the detosylated product (VIII) in satisfactory yields with these reagents at our hands. However, the recently reported procedure[10] using sodium in ethanol and tetrahydrofuran gave VIII in good yields. Thus, VII (1 mmol) was treated with sodium (2.5 mmol) in EtOH-THF (1:1) at 0-5° for 2 hr and then the reaction mixture allowed to attain room temperature and stirred for 3 hr. Usual work-up followed by column chromatography gave pure VIII in 70% yield, b.p. 128-30°/1.5 mm; IR (neat): 1320 and 1145 cm^{-1}; PMR (CCl_4): δ 1.56 and 1.63 [2s, 6H, $-CH=C(CH_3)_2$], 1.9 (*t*, 2H, C_4-H), 5.0 [*m*, 1H, $>CH=C(CH_3)_2$]. The IR and PMR spectral data of VIII were identical with those reported earlier[4] by us.

Two of us (A M S and A S P) thank CSIR, New Delhi for the award of research fellowships.

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Synthesis of 2,6-Dimethyl-1,6-hepta-dien-3-yl Acetate†

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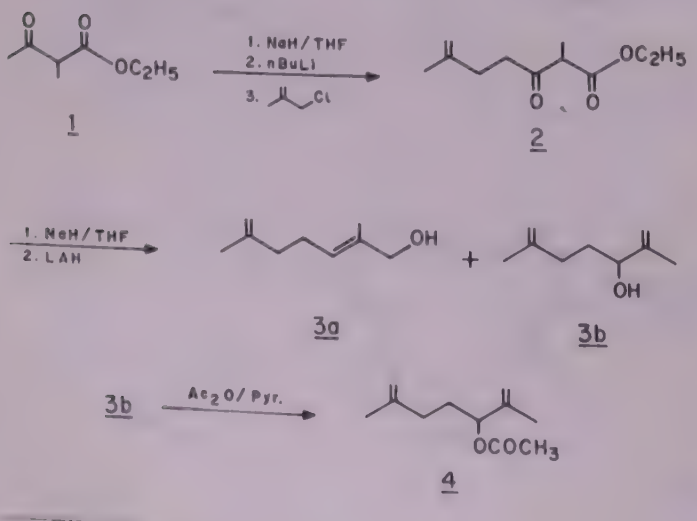
A convenient and short route for the synthesis of the title compound (4) starting from ethyl 2,6-dimethyl-3-oxo-hept-6-enoate (2) is described. 2 is treated with NaH in tetrahydrofuran and the resulting enolate on reduction with LAH affords the alcohol 2,6-dimethyl-1,6-heptadien-3-ol (**3b**) which on acetylation furnishes **4**.

2,6-Dimethyl-1,6-heptadien-3-yl acetate (**4**) is a potent insect sex attractant of comstock mealybug, *Pseudococcus comstocki* Kuwana, one of the most serious pests of apple, pear and other agricultural crops. In view of its high pheromone activity, a number of routes have been reported for its synthesis[1-4]. We now wish to report a new, short and straightforward synthesis of **4**, via the reaction sequence shown in Scheme 1.

Ethyl 2,6-*dimethyl*-3-*oxo*-*hept*-6-*enoate* (**2**)

To a suspension of prewashed sodium hydride (1.456 g, 30.3 mmol) in dry THF (60 ml) and dry hexamethylphosphoramide (13 ml) was added dropwise ethyl 2-methylacetoacetate (**1**) (4.32 g, 30 mmol) at 0° and stirred for 15 min under nitrogen. To this colourless solution 2.4 *M* *n*-butyllithium (12.5 ml, 30 mmol) was added at 0° and stirred for an additional 30 min. The resulting yellow to orange coloured solution of the dianion was reacted *in situ* with methallyl chloride (2.95 ml, 30.3 mmol) in dry THF (15 ml) at 0°C. The reaction mixture was stirred at room temperature for 3.5 hr and then quenched with saturated ammonium chloride solution (15 ml). The aqueous layer was extracted with ether (3 × 25 ml) and the combined organic extract washed with water, brine and dried (Na_2SO_4). The solvent was evaporated to give 5.22 g (88%) of pure **2**, b.p. 122-25°C/15 mm (lit.[7] 125-28°/18 mm); PMR($CDCl_3$): δ 1.28 (*t*, J=7 Hz, 3H, CH_3-CH_2), 1.3 (*d*, J=8 Hz, 3H, CH_3-CH), 1.7 (*s*, 3H, C_6-CH_3), 2.25 (distorted *t*, 2H, C−5 methylene), 2.64 (distorted *t*, 2H, $-CH_2-CO-$), 3.5 (*q*, J=7.5 Hz, 1H, $CHCH_3$), 4.14 (*q*, J=7 Hz, 2H, $-OCH_2CH_3$), 4.62 (*m*, 2H, $>C=CH_2$); IR(Neat): 1748, 1715 and 1650 cm^{-1}.



2,6-*Dimethyl*-1,6-*heptadien*-3-*ol* (**3b**)

To a stirred suspension of sodium hydride (0.6 g, 12.5 mmol, prewashed with dry light petroleum) was added a solution of **2** (1.5 g, 7.575 mmol) in dry THF (40 ml) and stirred at room temperature until evolution of hydrogen ceased (~2 hr). The resulting slurry was treated with lithium aluminium hydride (0.475 g, 12.5 mmol). The reaction mixture was refluxed for 3 hr, cooled and water (0.5 ml) added carefully. The solid was filtered and the filtrate concentrated *in vacuo* to give a mixture (0.998 g, 95%) of alcohols **3a** and **3b**. The mixture was separated on column chromatography on silica gel using pet ether-ethyl acetate (98:2) as an eluent which afforded 0.625 g of **3b** and 0.296 g of **3a**. The physical and spectral data of **3b** were identical with those reported in literature[1]; b.p. 118-20° (bath temp)/10 mm; PMR($CDCl_3$): δ 1.7 (*s*, 6H, $2CH_3$), 1.5-2.3 (*m*, 4H, $-CH_2-CH_2$), 4.0 (*t*, J=6 Hz, 1H, $-CH-OH$), 4.65 (*d*, J=1 Hz, 2H, $CH_2=C$), 4.9 (*m*, 2H, $>C=CH_2$); IR(Neat): 3360, 1650 cm^{-1}; PMR($CDCl_3$) of **3a**: δ 1.63, 1.72 (2*s*, 3H each, $2CH_3$) 1.9-2.4 (*m*, 4H, $-CH_2-CH_2-$), 3.9 (*s*, 2H, $-CH_2-OH$), 4.65 (*bs*, 2H, $>C=CH_2$), 5.3 (distorted *t*, $H'>C=C<$); IR(Neat): 3340, 1650 cm^{-1}.

2,6-*Dimethyl*-1,6-*heptadien*-3-*yl acetate* (**4**)

A solution of **3b** (0.1 g, 0.714 mmol), acetic anhydride (0.4 ml) and pyridine (0.4 ml) was stirred at room temperature for 2 hr. The reaction mixture was poured into ice-water and extracted with ether (3 × 2 ml). The ether extract was washed with dil. hydrochloric acid, water and brine and dried (Na_2SO_4). The solvent was removed *in vacuo* to give 0.125 g (96%) of **4**, b.p. 98-100°C (bath temp)/10 mm; IR(Neat): 1745, 1660, 1250 cm^{-1}; PMR($CDCl_3$): δ 1.65 (*s*, 6H, 2 × CH_3), 1.5-2.1 (*m*, 4H, $-CH_2-CH_2-$), 2.0

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(s, 3H, $COCH_3$), 4.6 (bs, 2H, $H_2C=C\lesssim$), 4.85 (bs, 2H, $H_2C-C\lesssim$), 5.1 (t, $J=6$ Hz, 1H, $\gtrsim CH-O-$).

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Meerwein Reduction of Levulinic Acid Derivatives: A New Route for the Synthesis of Glutamic Acid

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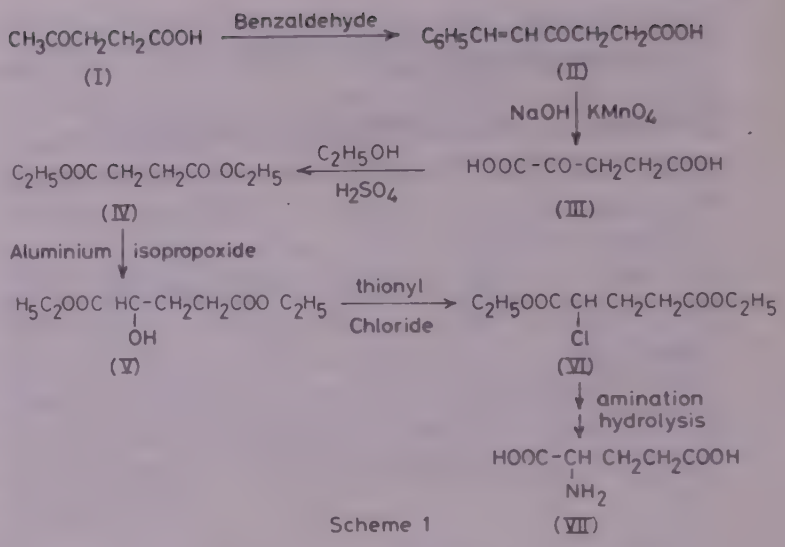
Glutamic acid has been prepared from levulinic acid by a new route. In this method, α, ketoglutaric (III) acid is obtained by oxidation of δ-benzallevulinic acid (II) and converted into diethyl ester (IV) which on Meerwein-Pondorff-Verley reduction furnishes the hydroxy derivative (V). The latter (V) is converted into chloro derivative (VI) which on amination gives glutamic acid (VII) in a good yield. Meerwein-Pondorff-Verley reduction of ethyl levulinate, ethyl β-bromolevulinate and 2,7-octanedione has also been studied. However, such a reduction of ethyl β-aminolevulinate remains unsuccessfull.

In continuation of our work on the syntheses of biochemicals and industrially useful compounds[1,2] we report herein the results of the little investigation leading to a new route for the synthesis of glutamic acid from levulinic acid.

Although the reduction with aluminium ethoxide as devised by Verley, Meerwein and Schmidt[3] is found applicable to several aldehydes only a few ketones can be reduced by this method. The Meerwein-Pondorff-Verley reduction which involves the use of aluminium isopropoxide is found to be a more satisfactory method for reducing ketones as well as aldehydes. This method has now been utilised for the reduction of various carbonyl compounds such as diethyl α-ketoglutarate, ethyl levulinate, ethyl β-bromolevulinate, ethyl β-aminolevulinate, and 2,7-octanedione.

Glutamic acid has been synthesised earlier by Fujise *et al.*[4] through pyridazine, by Motoki *et al.*[5] through β,δ-dibromolevulinic acid, and by phthalimide method. The presently worked out route for the synthesis of glutamic acid is shown in Scheme 1.



Scheme 1

The required benzallevulinic acid (II) was obtained by condensation of levulinic acid (I) with benzaldehyde. It was smoothly oxidised with alkaline potassium permanganate to afford α-ketoglutaric acid (III) in a good yield. The diethyl ester (IV) of III when subjected to Meerwein-Pondorff-Verley reduction gave diethyl α-hydroxyglutarate (V) which on treatment with thionyl chloride and pyridine furnished diethyl α-chloroglutarate(VI). The ester (VI) on amination with dry ammonia followed by hydrolysis with barium hydroxide and treatment with sulphuric acid afforded glutamic acid(VII).

During Meerwein-Pondorff-Verley reduction it was observed that although the reduction of ethyl levulinate, ethyl β-bromolevulinate, diethyl α-ketoglutarate and 2,7 octanedione gave good yields of the corresponding hydroxy compounds (65-80%), the reduction of ethyl β-aminolevulinate did not occur even after prolonged reaction. This may be due to the election donating ability of the amino group at α-position. Ethyl β-aminolevulinate was prepared from ethyl β-bromolevulinate by the action of dry ammonia.

All the chemicals used were chemically pure. Freshly prepared aluminium isopropoxide and isopropyl alcohol (BDH grade) were used in Meerwein-Pondorff-Verley reductions. The aluminium isopropoxide was prepared by dissolving amalgamated aluminium in anhyd. isopropanol. A solution (0.1%) of 2,4-dinitrophenylhydrazine (BDH grade) in water was used for testing acetone (negative if no cloudiness is formed within one-half min when 3 ml of the reagent is added to 5 drops of the distillate). All melting points and boiling points are uncorrected. IR spectra were recorded as smears (liquids) or as nujol mulls (solids) on a Perkin-Elmer 33 infrared spectrophotometer and 90 MHz PMR spectra on a Perkin-Elmer R-32 instrument using TMS as internal standard (chemical shifts in δ, ppm).

Benzallevulinic acid (II)

It was prepared by literature method[6] and crystallised from ethanol m.p. 125° (lit.[6] 126°); gave a 2,4-dinitrophenylhydrazone, m.p. 185° (lit. 186°) (Found: C, 71.2; H, 5.0 Calc. for $C_2H_{12}O_3$:C, 70.6, H,

†Part of Ph D Thesis of Uday R Joshi

5.9%); IR : 3090, 1700-1430, 755-690; PMR(TFA): 2.18(*m*, 2H, CH_2COOH), 3.9(*m*, 2H, $COCH_2$), 7.25(*m*, 5H, Ar−*H*) 6.9 and 7.95 (each *d*, 2H, −CH=CH).

Ketoglutaric acid (*III*)

A solution of II (20g) in NaOH (8g at 5% solution) was heated to 70° and hot potassium permanganate solution (4.8g in 200 ml water) added to it in instalments. When the solution became colourless, it was filtered hot, washed with hot water (3 × 50 ml), concentrated to 150 ml and acidified. The precipitated benzoic acid was filtered and clear solution evaporated to get a solid. It was crystallised from ethanol to give III, m.p. and m.m.p. 118°; 2,4-dinitrophenyl hydrazone: m.p. and m.m.p. 214°.

Treatment of III with ethanol and conce. sulphuric acid under reflux on a water-bath for 8-9 hr followed by usual work-up gave the diethyl ester (IV), b.p. 160°/30 mm (Found: ester value, 0.5664. Calc. ester value, 0.5544).

Diethyl α-hydroxyglutarate (*V*)

A mixture of IV (9 g), dry isopropanol (60 ml) and freshly prepared aluminiumisopropoxide (4 g.) was distilled at the rate of 1 drop per min with fresh addition of isopropanol (150 ml) as required. The distillate was tested for acetone with 2,4 dinitrophenyl-hydrazine. When no turbidity was obtained, the mixture was refluxed for 10 min, cooled and excess isopropanol removed under reduced pressure. Ether (100 ml) was added to the mixture and aluminium salt decomposed with HCl (2 *N*) while cooling under tap water. The ether layer was thoroughly washed with distilled water, dried (anhyd. Na_2SO_4), solvent removed and the residue distilled under reduced pressure to get V, b.p. 138°-40°/23-29 mm; IR : 3600-3000 (OH) 1750 and 1600 (ester CO).

Diethyl α-chloroglutarate VI

Thionyl chloride (3.5 ml) was added dropwise with stirring to V (3.5 g) and pyridine (1.8 g) while keeping the mixture cool. It was refluxed on a water-bath for 1 hr and ether (50 ml) and water (25 ml) were added to it with stirring. The ether layer was washed with water, dried (anhyd. Na_2SO_4), solvent removed and residue distilled under reduced pressure to get VI, b.p. 113-15°/12 mm (Found: Cl, 16.1. $C_9H_5O_4Cl$ requires Cl, 15.8%).

Glutamic acid (*VII*)

Dry ammonia was passed through a solution of diethyl α-chloroglutarate (6 g) in ethanol (60 ml) till saturated. The solution was filtered and excess of ammonia and ethanol were removed on a water-bath. It was filtered and refluxed with excess of barium hydroxide for 4 hr. The solution was filtered and concentrated on a water-bath. The barium salt obtained was decomposed by sulphuric acid (0.1 *N*) and barium sulphate filtered. The filtrate was concentrated and the amino acid (VII) precipitated by adding ethanol, washed with ethanol and dried, m.p. 230°, yield 1.29 g, identical in all respects with an authentic sample of VII.

Meerwein-Ponndorf-Verley reduction

(*i*) *Ethyllevulinate* : *Formation of ethyl α-hydroxyvalerate*

A mixture of ethyl levulinate (8 g), dry isopropanol and freshly prepared aluminium isopropoxide (3 g) was slowly distilled until the distillate did not give test for acetone with 2,4-DNP (3 hr). Thereafter, excess propanol was distilled under reduced pressure, sufficient ether added and the mixture decomposed with 2*N* HCl while cooling under tap water. The ether layer was washed with water, dried (anhyd. Na_2SO_4), solvent removed and the residue distilled under reduced pressure to give ethyl γ-hydroxyvalerate, b.p. 95°/20 mm, IR: 3,500(OH).

(*ii*) *Ethyl β-bromolevulinate* : *Formation of ethyl β-bromo-γ-hydroxyvalerate*

A mixture of ethyl β-bromolevulinate (4 g) and dry isopropoxid (2 g) was slowly distilled with fresh additions of dry isopropanol till the distillate gave negative ketone test with 2,4-DNP (3 hr). After the usual work-up as above the bromohydroxy ester (b.p.85°/7-8 mm) with slight decomposition was collected, yield 2.6g (Found:Br, 35.2. Calc for $C_7H_{12}O_3Br$: Br, 35.6%).

(*iii*) 2,7-*Octanedione* : *Formation of* 2,7-*octanediol*

A mixture of 2,7-octanedione (b.p.112°/12 mm, 2.5g), dry isopropanol (50 ml) and freshly prepared aluminium isopropoxide (1 g) was slowly distilled at the rate of two drops per min. After the usual work-up as described above 2.7-octanediol (b.p. 135-37°/12 mm, yield 1.5 g) was obtained; IR: 3500, 3000 (OH) (Found : C,66.1; H, 11.0. $C_8H_{14}O_2$ requires C, 65.7; H, 12.3%).

(*iv*) *Ethyl β-aminolevulinate*

Ethyl β-bromolevulinate was prepared by the method of Wolf[7]. Ethyl β-bromolevulinate (8g) was taken in anhyd. ethanol (50 ml) and dry ammonia gas passed through the cold solution till it became saturated with ammonia. The saturated solution was kept for 1 hr and ethanol removed under reduced pressure at 45-50°. The precipitated ammonium bromide was separated, washed with anhyd. ethanol (5

ml) twice and ether (anhyd.) added to precipitate the amino compound. It was filtered washed with ether and dried under vacuum at 40-50°, yield 4g (Found: N, 10.1. Calc. for $C_7H_{15}NO_2$: N, 9.7%).

Meerwein reduction could not be applied to ethyl β-aminolevulinate as even traces of acetone could not be detected after prolonged reaction and the original compound was recovered.

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Heterocycles: Part 3—Synthesis of Indolo[3,2-*h*]coumarins

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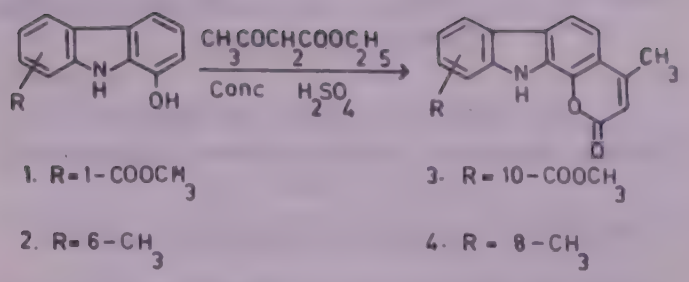
Methyl 8-hydroxycarbazole-1-carboxylate (1) and 1-hydroxy-6-methylcarbazole (2) have been condensed with ethyl acetoacetate in the presence of conc. sulphuric acid to afford indolo[3,2-*h*]coumarins (3) and (4), respectively.

Indolo[3,2-*h*]coumarins or pyrano[5,6-*a*]-2-one-carbazole derivatives can serve as intermediates towards synthesising 2,2-dimethyl-2H-pyrano[2,3-*a*]carbazole derivatives by Grignard reaction. Indolo[3,2-*h*]coumarins are hitherto unknown in nature, despite a possibility of their existence, and also have not been synthesised so far. The synthons for these are 1-hydroxycarbazoles, which were synthesised from 1-oxo-1,2,3,4-tetrahydrocarbazoles[1,2]. The results reported in this note are in continuation of our work[1,3].

In the present study, the Pechmann condensation[4] of methyl 8-hydroxycarbazole-1-carboxylate (1) and 1-hydroxy-6-methylcarbazole (2) with ethyl acetoacetate in the presence of conc sulphuric acid resulted in the formation of indolo[3,2-*h*]coumarins (3) and (4) respectively. Their structural assignments were supported by PMR and IR spectroscopy and elemental analyses.

Methyl 2*H*,11*H*-*indolo*[3,2-*h*]-4-*methylcoumarin*-10-*carboxylate* (3)

A solution of 1 (0.482 g, 0.002 mol) in ethyl acetoacetate (3 ml) was added dropwise to precooled



(0-10°C) conc sulphuric acid (15 ml). The reaction mixture was stirred and allowed to attain room temperature after 1 hr. It was kept at room temperature for 24 hr and poured onto crushed ice. The separated solid on crystallisation (MeOH) gave yellow crystals of **3**, m.p. 285°, yield 450 mg (73%); IR(nujol): 3450 (>N−H), 1750-1700 cm^{-1} (*br*, lactone >C=O and ester >C=O); PMR($CDCl_3$/TMS): δ 2.56 (*d*, 3H, *J* = 1 Hz, C_4-CH_3), 4.4 (*s*, 3H, $C_{10}-COOCH_3$), 6.33 (*d*, 1H, *J* = 1 Hz, C_3-H), 7.4 (*m*, 2H, C_5-H and C_8-H), 7.94 (*d*, 1H, *J* = 8 Hz, C_6-H), 8.24 (*m*, 2H, C_7-H and C_9-H) and 10.2 (*br*, *s*, 1H, N*H*, D_2O exchangeable) (Found: C, 70.1; H, 4.1; N, 4.5. $C_{18}H_{13}NO_4$ requires C, 70.4; H, 4.3; N, 4.6%).

4,8-*Dimethyl*-2*H*,11*H*-*indolo*[3,2-*h*]*coumarin*(4)

It was prepared in a similar manner starting from 2 and the product was crystallised (MeOH) as greenish dark yellow needles, m.p. 265-66°, yield 240 mg (45%); IR(nujol): 3250 (NH), 1740 (lactone >C=O); PMR($CDCl_3$/TMS): δ 2.48 (*s*, 3H, C_8-CH_3), 2.58 (*d*, 3H, C_4-CH_3, *J* = 1 Hz), 6.2 (*d*, 1H, C_3-H, *J* = 1 Hz), 7.1 (*m*, 4H, C_5-H, C_6-H, C_9-H and $C_{10}-H$), 7.85 (*s*, 1H, C_7-H) and 8.4 (*br*, *s*, 1H, NH, D_2O exchangeable) (Found: C, 77.3; H, 4.8; N, 5.1. $C_{17}H_{13}NO_2$ requires C, 77.6; H, 5.0; N, 5.3%).

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One-Pot Synthesis of 2,3-Disubstituted Quinazolin-4-ones

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Whereas the condensation of N-acetylanthranilic acid (**1a**) with methyl and phenyl isothiocyanates (**2**) affords the corresponding 3-substituted 2-methylquinazolin-4-ones (**7**, R^1 = Me), N-benzoylanthranilic acid (**1b**) reacts with these isothiocyanates to give 2-phenyl-3,1-benzoxazin-4-one (**5b**; R^1 = Ph) and N-substituted *o*-benzoylaminobenzamide (**6**; $R^1 = R^2$ = Ph), respectively.

Carboxylic acid react with alkyl and/or aryl isothiocyanates to give the corresponding N-substituted amides[1,2]. In order to explore the synthetic utility of this reaction further, we have now studied the reaction of N-acylanthranilic acids (**1**) with methyl and phenyl isothiocyanates (**2a,b**) using pyridine as a catalyst. In the case of N-acetylanthranilic acid (**1a**), the corresponding quinazolones (**7**) were the main products. However, N-benzoylanthranilic acid (**1b**) afforded 2-phenyl-3,1-benzoxazin-4-one (**5b**; R^1 = Ph) and N-phenyl-*o*-benzoylaminobenzamide (**6**; $R^1 = R^2$ = Ph) respectively.

As shown in Scheme 1, the reaction can follow two different routes. The formation of benzoxazinones (**5a** and **5b**) from **1** and **2** was indicated by TLC (silica gel/benzene), and 2-phenyl-3,1-benzoxazinone (**5b**; R^1 = Ph) was actually isolated in moderate yields from the reaction of **1b** with **2a**. Though **5** could be generated by thermal cyclodehydration of **1**, this would not explain the formation of **6** and/or **7** for which the presence of an amine in the reaction mixture is necessary. Since isothiocyanates are stable even in the presence of steam, their decomposition by water is ruled out. The formation of **5** indicates that path-A does not predominate. It should be mentioned that **5b** (R^1 = Ph) unlike **5a** (R^1 = Me) is sufficiently stable and possibly that is the reason why it remained unaffected by methyl amine which escaped under the reaction conditions. However, the reaction of **1b** with **2b** afforded **6** ($R^1 = R^2$ = Ph) which is known to undergo cyclisation to **7** ($R^1 = R^2$ = Ph) at a much higher temperature[3]. The products were prepared by an alternative route, as shown in Scheme 1, and characterised by spectral data. These compounds are generally obtained by multi-step synthesis[3], but in the present method all the steps can be carried out in the same pot.

Reported melting points are uncorrected. IR spectra were recorded in nujol on a Perkin-Elmer-720 spectrophotometer.

Reaction of N-acylanthranilic acids with methyl/phenyl isothiocyanates (**2**): *General procedure*

A mixture of **1** and **2** in a molar ratio of 1:1.2 was heated for 30 min with pyridine as a catalyst. The temperature was maintained at 130-40° in the case of methyl isothiocyanate (**2a**) and at 160-70° for phenyl isothiocyanate (**2b**). The reaction mixture, after washing with aq. $NaHCO_3$ and cold water, was taken

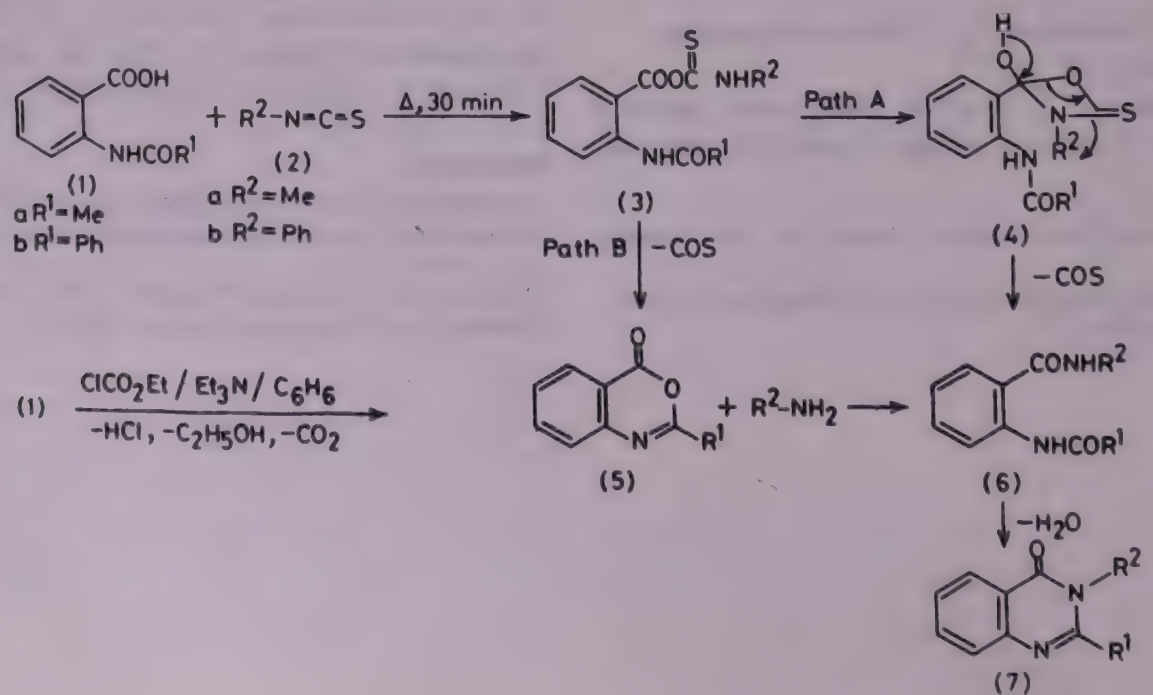

Table 1— Reaction of N-Acylanthranilic Acids (1) with Methyl/Phenyl Isothiocyanates (2)

Reactants	Product*	R^1	R^2	Yield (%)	m.p. °C
1b + 2a	5	Ph	—	30	123-25[4]
1b + 2b	6	Ph	Ph	55	275-77[5,6]
1a + 2a	7a†	Me	Me	28	70-72[7,8]
1a + 2b	7b‡	Me	Ph	54	146-48[9]

*The corresponding 3,1-benzoxazin-4-one (5) was discernible by TLC.

†Recrystallised from water.

‡Recrystallised from aq. ethanol.

up in benzene from which benzoxazinone (5) and quinazolone (7) were obtained on removing the solvent under suction. The benzene-insoluble part afforded 6. The products, except 5b (R^1 = Ph) which was purified by TLC over silica gel using methylene chloride-benzene (1:1) as irrigant, were generally pure. Quinazolones (7) were recrystallised from water or aq. ethanol. Relevant physical data are given in Table 1.

We thank CSIR, New Delhi for the award of a senior research fellowship to one of us (RA).

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Preparation of Some Dihydroxamic Acids & Their Reaction with Benzenesulphonyl Chloride

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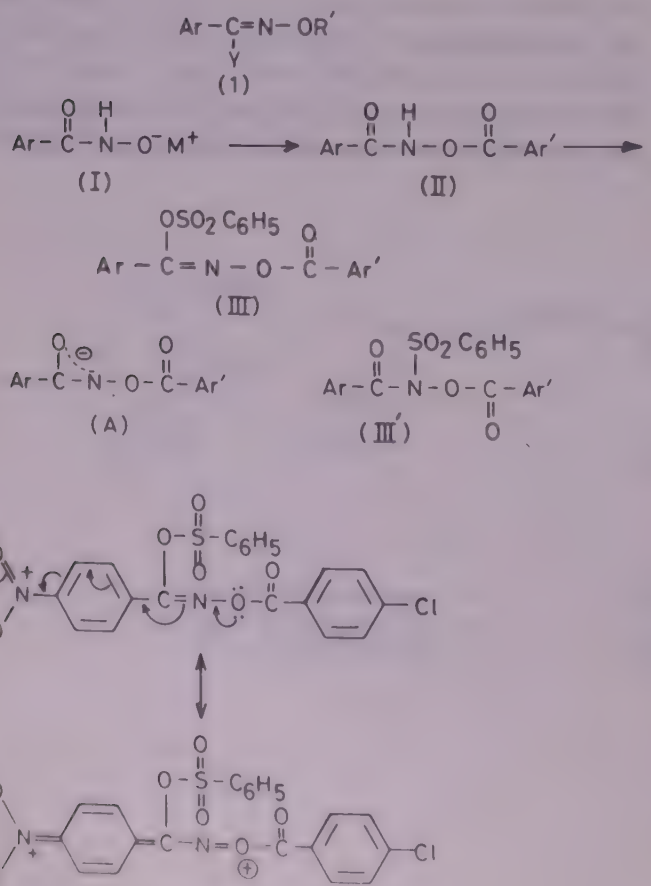
Several dihydroxamic acids (II) have been prepared and reacted with benzenesulphonyl chloride in dioxane below 10°C in the presence of triethylamine to yield the corresponding imino-ether type of compounds (III). The structure elucidation of II and III is based on their spectral data.

The literature monitoring programme recently conducted by the Cancer Research Institute, NIH, Maryland has identified several compounds belonging to the series **1** as potential anti-cancer agents[1]. Dihydroxamic acids of the type N-acyl-O-acyl-hydroxylamine (II) are also expected to afford iminoethers of the type III which may show anti-cancer activity. We were therefore prompted to undertake the synthesis of III with a view to screening their anticancer activity in collaboration with NIH, Maryland.



Iminoethers are useful starting materials for the preparation of amidines, hydroxamic alkylethers and thioesters[2]. Among the various methods available for the synthesis of iminoether type compounds, the present method involving direct treatment of II with aromatic sulphonyl chloride in the presence of a base appears to be clean and easy to handle.

The reaction of N-acyl-O-acyl-hydroxylamines (II, Table 1) with benzenesulphonyl chloride did not occur in the absence of a base even when the reaction mixture was heated. However, the reaction proceeded smoothly at 0° in the presence of a catalytic amount of Et_3N. The reaction was therefore carried out within a temperature range 0-10° and it was ensured in a separate experiment that at this temperature, none of the dihydroxamic acids decomposed to give Lossen-rearrangement products. In fact, for Lossen rearrangement to occur, dihydroxamic acids require heating at higher temperature for a longer period. This tends to indicate that II reacts with base at low temperature to give the ambident anion **A**, which reacts with benzenesulphonyl chloride to give the product (III; Table 1). Reactions of various ambident anions other than those derived from N-acyl-O-alkylhydroxylamines and N-acyl-O-acylhydroxylamines have been investigated by Kornblum and coworkers[3]. Misra *et al.*[4] have reported the reactions of ambident anions derived from N-acyl-O-alkylhydroxylamines with aromatic sulphonyl chlorides.

The ambident anion **A** has two active sites where benzenesulphonyl group may be attached. This raises the question of orientation of benzenesulphonyl group

Table 1—Physical Data of Dihydroxamic Acids (II) and Iminoethers (III)

Compound	Ar	Ar	m.p.	(%) Yield
IIa	C_6H_5	C_6H_5	160-61	90
IIb*	p-$NO_2C_6H_4$	C_6H_5	165-66	90
IIc	C_6H_5	2-Pyridyl	155-66	82
IId†	p-ClC_6H_4	p-$NO_2C_6H_4$	140-41	75
IIe	p-$NO_2C_6H_5$	p-ClC_6H_4	157-58	80
IIf‡	p-$CH_3O.C_6H_4$	p-ClC_6H_4	120-21	82
IIg**	m-$NO_2C_6H_4$	p-$Cl.C_6H_4$	160-61	78
IIIa	p-$CH_3O.C_6H_4$	p-$Cl.C_6H_4$	115	60
IIIb	m-$NO_2C_6H_4$	p-$Cl.C_6H_4$	111-12	64
IIIc	p-$NO_2C_6H_4$	C_6H_5	160	60
IIId	p-$NO_2C_6H_4$	p-ClC_6H_4	119	50

*UV: 375 nm (ε_{max} 76.5).
†UV: 360 nm (ε_{max} 63).
‡UV: 350 nm (ε_{max} 30.5).
**UV: 350 nm (ε_{max} 58).

on the ambident anion and all the theories propounded by Kornblum and coworkers[3] concerning orientation of alkyl group on the ambident anion should be valid. The products having structures III and III′ may result from the reaction of benzenesulphonyl chloride with A.

However, on the basis of IR and PMR spectral studies the products were found to have structure III. The IR spectra exhibited absorption bands at 1780 (ester carbonyl), 780 (aromatic), 1180 (SO_2) and 1590 cm^{-1} (C=N) in conformity with the structure III. The PMR spectra of the products displayed signals only in the aromatic region and therefore these spectra were not of much help in deciding between the structures III and III′.

The visible and UV spectral studies also supported the structure III. O-Benzenesulphonyl-N-*p*-chlorobenzoyloxy-*p*-nitrobenzoiminoether showed a λ_{max} in ethanol at 345 nm indicating the extended conjugation which is possible in the case of III.

No such extended conjugation is possible in compounds having the sulphonamide type structure III′.

Melting points were determined in open capillaries and are uncorrected. Benzenesulphonyl chloride (BDH) was distilled before use. Triethylamine (LR grade) was used without further purification. IR spectra were taken in nujol mull.

Visible spectra were recorded on a Bausch-Lomb Spectronic-20 spectrophotometer and PMR spectra in $CDCl_3$ on a Jeol FT-100 instrument using TMS as internal standard.

TLC was performed on plates coated with silica gel-G using benzene-ethyl acetate (1:1) as irrigant; spots were developed in an iodine chamber. The progress of all the reactions was monitored by TLC.

Potassium benzohydroxamate was prepared by the modified method of Hauser and Renfrow[5].

Barium salt of m-nitrobenzohydroxamic acid

To an ethanolic solution of potassium *m*-nitrobenzohydroxamate was poured three times its volume of water and the mixture stirred until a clear solution was obtained. Any salt that had precipitated from the alcoholic solution was dissolved in the alcohol-water solution. The solution was made acidic with conc. HCl and to it barium chloride ($BaCl_2.2H_2O$) (40.8 g, .167 mol) added. Addition of conc. ammonia solution produced a dense precipitate of barium salt of *m*-nitrobenzohydroxamic acid which was filtered, washed with water and allowed to dry in air, yield 55%.

O-Benzoyl-p-nitrobenzohydroxamic acid (IIa)

The compound was prepared by the modified method of Renfrow *et al.*[6]. To a suspension of *p*-nitrobenzohydroxamate (0.05 mol, 11 g) in 10 ml of dioxane was added benzoyl chloride (0.05 mol, 7.9 g) and the reaction mixture refluxed for 10 min in an oil-bath, cooled to room temperature and poured in water (500 ml). The precipitated IIa was filtered and recrystallized from ethanol, yield 90%, m.p. 164-65°; IR: 3300 (−NH−), 1750 (ester C=O), 1670 (−CO−NH−), 1540 ($-NO_2$) and 760 cm^{-1} (aromatic). Its PMR spectrum exhibited a multiplet at δ 8.24 due to only aromatic protons. Its UV-visible spectrum in dioxane showed a λ_{max} at 375 nm.

Other dihydroxamic acids were also prepared by the above procedure and their physical data are given in Table 1.

Reaction of dihydroxamic acids with benzenesulphonyl chloride: Formation of iminoethers III (Table 1)

Method (A)

An equimolar mixture of II and benzenesulphonyl chloride in dioxane (10 ml) was kept in the cold and then heated with stirring for 1 hr. No precipitation was observed and TLC of the reaction mixture did not show any change.

Method (B)

To O-*p*-chlorobenzoyl-*p*-nitrobenzohydroxamic acid (IId) (0.32 g, 0.001 mol) in dioxane (10 ml) were added 2-3 drops of triethylamine and reaction mixture was stirred at room temperature until a clear solution was obtained. To it was added benzenesulphonyl chloride (0.176 ml, .001 mol) in the cold and the solution stirred for 15 min. The product benzenesulphonyl-N-*p*-chlorobenzoyloxy-*p*-nitrobenziminoether (IId, Table 1) which precipitated as a white powder, was filtered under suction and recrystallized from dry ethanol, yield 60%, m.p. 110-11°, IR: 1775 (−O−CO−), 1180 ($-SO_2$), 1590 (−C=N) and 780 cm^{-1} (aromatic); UV-Vis :345 nm.

Similarly other compounds of the series III were prepared. Their physical data are given in Table 1.

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Novel Method for Nitration & Polymerisation of Symmetric Trihydroxybenzene Using Ceric(IV) Ammonium Nitrate

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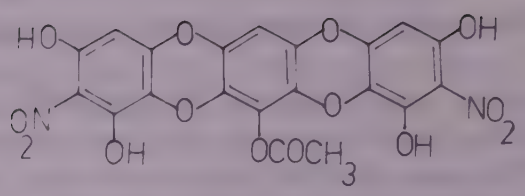
Only symmetric isomer of trihydroxybenzene (phloroglucinol) on treatment with cerium (IV) ammonium nitrate produces 13-acetoxy-1,3,9,11-tetrahydroxy-2,10-dinitrobenzo[1,2-*b*:4,5-*b*]bis-[1,4]benzodioxin (I) along with 1,3-dihydroxy-5-methoxy-2-nitrobenzene, 1,3,5-trihydroxy-2-nitrobenzene and 1,5-dihydroxy-3-methoxy-2-nitrobenzene, while other isomers undergo very rapid reaction with the formation of polymers which are difficult to separate.

Cerium(IV) ammonium nitrate (CAN) has recently been used as a nitrating agent[1,2] but a systematic study on its reaction with phenolics has not been carried out so far. In the present investigation, we have studied the reaction of CAN with different isomeric trihydroxybenzenes and the results are reported in this note.



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1,3,5-trihydroxybenzene on reaction with CAN yielded a polymeric compound (**A**) with nuclear acetoxylation (structure I) along with nitromethoxy isomers (**B**, **D**) and 1,3,5-trihydroxy-2-nitrobenzene (**C**). The other two isomers of trihydroxybenzene showed very spontaneous reaction with CAN with the formation of polymers which were difficult to separate.

Out of four compounds obtained from the reaction of phoroglucinol with CAN, the polymeric compound (**A**) showed strong absorptions at 2950, 1585, 1385, 1380 and 1320 cm^{-1} in its IR spectrum revealing the presence of aromatic nitro group. Its PMR spectrum revealed the presence of ten different protons (Table 1). Its mass spectrum showed a molecular ion peak at *m/z* 502 followed by strong peaks at *m/z* 428, 354 and 280 indicating the successive loss of 74 mass units which could be attributed to the loss of NO_2 and CO groups

Table 1—Characterization Data of Various Products Obtained

Product	Yield (%)	Physical state	m.p.* °C	Mol. formula (M^+)	PMR (δ, ppm)	Derivative (m.p., °C)
13-acetoxyl-1,3,9,11-tetra-hydroxy-2,10-dinitrobenzo-[1,2-*b*:4,5-*b*']bis[1,4]-benzodioxin (I; **A**)†	40	Orange yellow plates	128-30	$C_{20}H_{10}N_2O_{14}$ (502)	$CDCl_3$: 10.4 (*s*, 4H; four Ar-O*H*), 7.3 (*s*, 2H; two Ar-*H*), 7.1 (*s*, H; Ar-*H*), 2.3 (*s*, 3H; (*s*, 3H; Ar $OCOCH_3$)	
1,3-Dihydroxy-5-methoxy-2-nitrobenzene (**B**)	15	Orange yellow needles	141-43 (153-54)[3]	$C_7H_7NO_5$ (185)	$CDCl_3$: 10.05 (*s*, 2H; two Ar-O*H*), 7.32 (*m*, 2H; two Ar-O*H*), 3.89 (*s*, 3H; $ArOCH_3$),	Acetate (119)
1,3,5-trihydroxy-2-nitrobenzene (**C**)	20	Red needles	180-82 (183-85)[4]	$C_6H_5NO_5$ (171)	(CD_3COCD_3): 6.70 (*m*, 1H 6.0 (*s*, 4H) No prominent signal was observed after 0.5 hr of the addition of D_2O	Acetate (107-8) Trimethyl ether (151-52)
1,5-Dihydroxy-3-methoxy-2-nitrobenzene (**D**)	20	Orange yellow needles	171-73 (187)[3]	$C_7H_7NO_5$ (185)	($CDCl_3 + CD_3OD$): 7.30 (*m*, 2H) 6.03 (*s*, 2H; two Ar-O*H*), 4.20 (*s*, 3H; Ar-OCH_3)	Acetate, (77)

*Literature m.ps are given in parentheses.
†IR(KBr): 3250 (OH), 2950, 1585 (Ar, C=C), 1645 (C=O), 1555, 1320 cm^{-1} (NO_2).

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from the molecular ion. A weaker peak at *m/z* 294 could be due to the loss of acetic acid molecule from the peak at *m/z* 354 while the peak at *m/z* 340 could be assigned to the loss of $-NO_2$ group and a ketone molecule from the peak at *m/z* 428. A strong peak at *m/z* 221 could be due to the loss of acetoxyl function from the fragment at *m/z* 280. The peak at *m/z* 252 was assignable to the loss of a ketene (CH_2CO) molecule from *m/z* 204 fragment. The peaks corresponding to *m/z* 126, 125 and 123 could be assigned to the phloroglucinol nucleus, (phloroglucinol nucleus-H) and (phloroglucinol nucleus-3H) respectively. The strong peak at *m/z* 97 was due to the loss of (CO + H) from the peak at *m/z* 126, and the other strong peak at *m/z* 69 was due to the loss of CO from the peak at *m/z* 97. The peak at *m/z* 147 could be due to the loss of CO and NO_2 from the peak at *m/z* 221. Based on these evidences and PMR spectral data, the structure of compound-A was established as 13-acetoxy-1,3,9,11-tetrahydroxy-2,10-dinitrobenzo[1,2-*b*:4,5-*b*′]bis-[1,4]benzodioxin (I).

Melting points were taken in open capillaries on an electric melting point apparatus and are uncorrected. IR spectra recorded on Perkin-Elmer 237 and 577 spectrophotometers, PMR spectra on a Varian A60 spectrophotometer using TMS as internal standard, and mass spectra on a JEOL-JMS D-300 instrument.

Procedure

Phloroglucinol (1 g) was dissolved in a mixture of acetic acid and methanol (1:1; 30 ml) and a strong solution of CAN (2.5 g in 20 ml) in the same solvent added to it. The reaction mixture was heated for 30 min on a water-bath, cooled, poured into crushed ice (250 g) and extracted repeatedly with chloroform. The organic extracts were mixed, concentrated under reduced pressure and subjected to column chromatography on silica gel using pet. ether (b.p. 60-80°), benzene and ethyl acetate as eluents. Four products (**A**, **B**, **C** and **D**) were obtained in pure state and three of them identified by their spectral data, physical constants, preparation of their suitable derivatives and finally by comparison with authentic samples (Table 1).

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Collision Induced Dissociation Study of $C_7H_8N^{7+}$ from N-Phenylphenoxyacetamide

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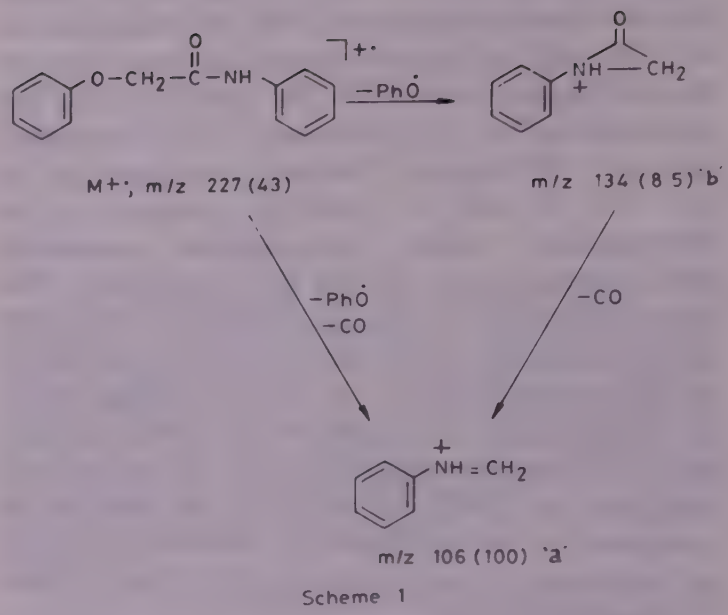
It has been shown by collision induced dissociation studies that the ion at *m/z* 106 ($C_7H_8N^+$) in the mass spectrum of N-phenylphenoxyacetamide has a structure similar to that of $M-N^{7+}$ from N-methylaniline and $M-CH_3^{7+}$ ion from N-ethylaniline.

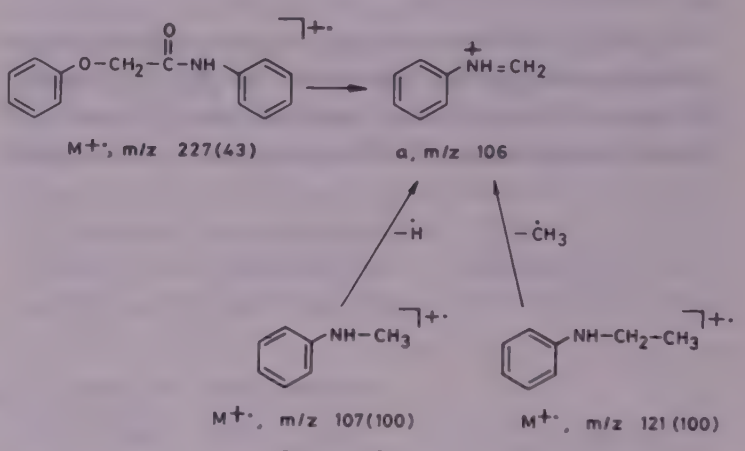
The mass spectra of phenoxyacetyl derivatives show interesting rearrangements[1-3]. Recently we have studied the mass spectrum of phenyl phenoxyacetate (**1**), S-phenyl phenoxythioacetate (**2**) and N-phenylphenoxyacetamide (**3**) and shown by collisionally induced dissociation (CID) studies that in **3** the ion at *m/z* 108 has more than one structure, the major being that of molecular ion of anisole[4]. We also reported[5] that the most intense ion $C_6H_5X^+{=}CH_2$(a) (X = O, S or NH) in **1**, **2** or **3** is formed by successive loss of CO and phenoxy radical in **1** and **2** and by the loss of phenoxy radical followed by the elimination of CO in **3**. With a view to examining the structure of ion (a) corresponding to $C_7H_8N^{7+}$ (*m/z* 106) in **3** which is mechanistically interesting, the CID studies of this ion have now been undertaken.

The N-methylaniline and N-ethylaniline were commercial samples (purity 98% by GC) and used as such. N-Phenylphenoxyacetamide was prepared by literature method[5]. The mass spectra were recorded on a VG Micromass 70-70H mass spectrometer at 70eV with an emission current of 200 μA. The source temperature was 180°C. Liquid samples were introduced through heated reservoir inlet and the solid samples through direct inlet probe. Metastable decomposition in the first field free region was recorded by linked scan technique (B/E constant). Helium was used as the collision gas and the pressure of He was adjusted so that the intensity of the main beam was reduced to 40-50% of its original intensity. Corrections for the metastable decomposition in CID were made as per the procedure of Tilborg and Thuijl[8].

The mechanism of formation of (a) in **3** is shown in Scheme 1. Though one would expect the structure (a) to be more stable, in the absence of conclusive evidence for establishing the structure of ion (b), the structure of (a) remains inconclusive. However, CID being a powerful tool to study the structures of gaseous ions, ions like (a) can be generated from knwon precursors and their CID compared. The $M-H^{7+}$ from N-methylaniline (**4**) and $M-CH_3^{7+}$ from N-ethylaniline (**5**) are expected to have structure (a) if they are produced by simple cleavages (Scheme 2). However, recently it has been shown by D-labelling studies that



Scheme 1



Scheme 2

Table 1—MI Spectra of *m/z* 106 from **3**, **4** and **5**[a]

m/z	3	4	5
105	16	4	4
104	11	14	14
80	1	1.4	1.6
79	53	75	70
78	7	3	4
77	12	3	5

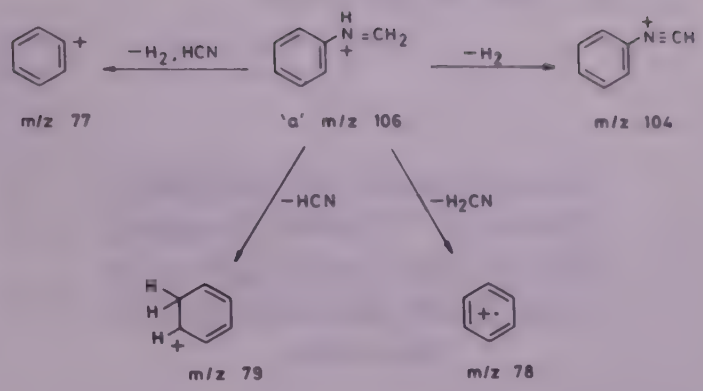
(a) Intensity given as percentage of the total ionization of all the daughter ions.

Table 2—CID Spectra of m/z 106 from **3**, **4** and **5**[a]

m/z	3	4	5
105	12.6	11.0	13.0
104	23.1	27.0	27.7
103	0.6	0.4	0.3
102	0.4	0.5	0.3
92	0.5	0.4	0.4
91	0.8	1.0	0.8
90	0.4	0.3	0.4
89	—	0.3	0.2
80	0.5	0.5	0.3
79	8.5	13.4	9.9
78	8.6	9.1	9.1
77	29.7	23.3	24.0
76	4.1	3.6	3.8
75	1.4	1.2	1.3
74	1.5	1.3	1.2
65	1.0	1.0	0.6
64	0.4	0.4	0.3
63	1.2	1.1	1.2
62	0.7	0.5	0.5
52	0.7	0.5	0.6
51	2.0	1.6	2.0
50	1.3	1.1	1.4

(a) Intensity given as percentate of the total ionization of all the daughter ions.

(a) is formed from **4** not by simple cleavage but by rearrangement[6]. Hence, it is contemplated to compare the CID spectra of $M-H^{\neg 7+}$ from **4** and $M-CH_3^{7+}$ from **5** with that of (a). The metastable ion (MI) spectra of the ion at m/z 106 from **3**, **4** and **5** (Table 1) show that **4** and **5** are closely similar suggesting that decomposing ions under discussion are like in **4** and **5** and are different from that of **3**. The MI spectra have peaks characteristic of the structure (a). However, differences in the intensities of metastable ions cannot be



Scheme 3

attributed to different structures as the metastable ion spectra are internal energy dependent[7]. Hence, the CID spectra of non-decomposing ions from **3**, **4** and **5** have been analysed and the CID spectra corrected for unimolecular decomposition are shown in Table 2. The close similarity between the CID of the ion at m/z 106 from **3**, **4** and **5** proves that they all have common structure (a). The major ions in the CID spectra are as shown in Scheme 3, and these are in agreement with the proposed structure.

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Reexamination of Substituent Effects on ^{13}C NMR Chemical Shifts of Side-Chain Carbons in 5-Aryl-2*E*,4*E*-pentadienoic Acid Derivatives

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A careful analysis of the published ^{13}C NMR chemical shifts of the side-chain carbons in 5-aryl-2*E*,4*E*-pentadienoic acid methyl esters and in the corresponding piperidides [*Indian J Chem*, **23B** (1984) 546] reveals that the dual substituent parameter treatment gives excellent correlations for all the side-chain carbons. The observed reverse substituent effect for C-3 and C-5 carbons is explicable in terms of 'localized σ-polarization' mechanism.

In a recent paper Banerji *et al.*[1] have corrleated the ^{13}C NMR chemical shifts of the side-chain carbons in two series of 5-aryl-2*E*,4*E*-pentadienoic acid derivatives, viz. the methyl esters and piperidides with substituent constants σ^+ or σ^0. A reexamination of their data became necessary for the following two reasons: (i) The authors did not undertake a systematic correlation analysis of the substituent chemical shifts. In several cases, it has been observed that single parameter relationship does not give satisfactory correlations and hence in recent years dual substituent parameter (DSP) extensions of the Hammett approach are employed in corrleations with NMR chemical shifts[2]. Since the ρ_I and ρ_R values derived from DSP treatment give a direct measure of the relative transmission of inductive and resonance effects, it is desirable to apply the DSP treatment to the data reported. (ii) Banerjee *et al.*[1] also stated the reasons for the reverse substituent effects observed for C-3 and C-5 carbons but these are not final and the ^{13}C NMR data of these carbons are still a subject of investigation. In view of the recent investigations by Bromilow *et al.*[3] on reverse substituent effects of unsaturated systems in conjugation with an aromatic ring, a reasonable explanation is possible for the reverse substituent effects in arylpentadienonic acid derivatives.

The chemical shift data for C-2, C-3, C-4 and C-5 carbons in the case of methyl esters (series I) and piperidides (series II) were statistically corrleated with the substituent constants, σ, σ^+ and σ^0. Only the results of correlations with those substituent constants which yield least standard error and best correlation coefficients are presented in the form of regression equations in Table 1. The precision coefficient is given in terms of 95% confidence limit. The results of correlations are in striking contrast to the earlier report[1] wherein good correlations were observed for C-2 and C-4 with σ^+ and C-3 with σ^0 in both the series.

Considerable efforts are currently being made in the direction of a more quantitative interpretation of the reaction constants by employing the DSP treatment[4]. The DSP analysis of the chemical shift data were carried using the Ehrenson, Brownlee and Taft equation[5] (Eq. 1). The σ_I and σ_R values

$$\Delta\delta = \rho_I\sigma_I + \rho_R\sigma_R \qquad \ldots (1)$$

were taken from the compilation of Dayal *et al.*[6]. The correlations were performed for each of the resonance scales (σ_R^0, $\sigma_R^{(BA)}$, σ_R^+ and σ_R^-). Analyses of the multiple regression with various values of σ_R indicate that excellent correlations with the least standard error are obtained for all the carbons of the side-chain in both the series when the combination of σ_I and $\sigma_R^{(BA)}$ is employed. The results of the DSP treatment are presented in Table 2.

The striking feature of the DSP treatment is the observation of negative sign for ρ_I and ρ_R for C-3 and

Table 1—Correlation of ^{13}C NMR Chemical Shifts for Series I and II

		SE	r	n
	Series I			
δ_{C-2} =	3.47σ + 120.40 (±0.433)	0.259	0.992	9
δ_{C-3} =	−1.678 σ + 144.49 (±0.118)	0.071	0.997	9
δ_{C-4} =	5.241 σ + 125.52 (±0.799)	0.478	0.986	9
δ_{C-5} =	−3.452 σ^0 + 139.76 (±0.601)	0.298	0.982	9
	Series II			
δ_{C-2} =	3.532 σ + 120.45 (±0.539)	0.323	0.986	9
δ_{C-3} =	−1.134 σ^+ + 141.45 (±0.176)	0.165	0.985	9
δ_{C-4} =	5.092 σ + 126.30 (±0.780)	0.466	0.986	9
δ_{C-5} =	−3.441 σ^0 + 137.49 (±0.440)	0.218	0.990	9

SE = Standard error of the estimate; r = Correlation coefficient; n = Number of data points

Table 2—DSP Analysis of ^{13}C NMR Chemical Shifts for Series I and II

Series I							
$\Delta\delta_{C-2}=$	3.60 (±0.25)	$\sigma_I+4.02$ (±0.19)	$\sigma_R^{(BA)}-0.115$	0.998	0.154	99.9%	7
$\Delta\delta_{C-3}=$	−1.79 (±0.06)	$\sigma_I-1.55$ (±0.04)	$\sigma_R^{(BA)}-0.017$	0.999	0.035	99.9%	7
$\Delta\delta_{C-4}=$	4.84 (±0.44)	$\sigma_I+5.82$ (±0.34)	$\sigma_R^{(BA)}-0.088$	0.997	0.267	99.9%	7
$\Delta\delta_{C-5}=$	−4.00 (±0.23)	$\sigma_I-1.59$ (±0.18)	$\sigma_R^{(BA)}-0.162$	0.996	0.144	99.9%	7
Series II							
$\Delta\delta_{C-2}=$	3.92 (±0.37)	$\sigma_I+3.63$ (±0.28)	$\sigma_R^{(BA)}+0.071$	0.995	0.225	99.9%	7
$\Delta\delta_{C-3}=$	−1.31 (±0.30)	$\sigma_I-2.11$ (0.23)	$\sigma_R^{(BA)}+0.154$	0.987	0.182	99.9%	7
$\Delta\delta_{C-4}=$	5.25 (±0.60)	$\sigma_I+5.38$ (±0.46)	$\sigma_R^{(BA)}+0.048$	0.994	0.369	99.9%	7
$\Delta\delta_{C-5}=$	−3.62 (±0.23)	$\sigma_I-2.00$ (±0.18)	$\sigma_R^{(BA)}+0.015$	0.996	0.141	99.9%	7

R = Multiple correlation coefficient; SE = Standard error of the estimate; CL = Confidence level; n = Number of data points.

C-5 carbons indicating the reverse substituent effect i.e. electron-withdrawing substituents cause anupfield shift instead of down field. It has been recently demonstrated that in *para*-substituted compounds of the type $X-C_6H_4-\overset{\alpha}{C}H=\overset{\beta}{C}H$, the C-α carbon gives almost a constant ρ_I value[3,7-10] around −3.8. The ^{13}C NMR data on C-5 (corresponding to C-α) in series I leads to $\rho_I=-4.00$ and $\rho_I=-3.62$ in series II. The negative sign and near constancy of ρ_I values support the proposition of Bromilow *et al.*[3]. In this system π-polarization is the major contributor to the inductive component of C-5 and this type of polarization is the 'localized polarization' involving separate polarizations of ethenyl and phenyl π-systems. Polarization of conjugated π-system as a whole does not play a significant role in the determination of ρ_I value. The ρ_I value of C-3 is also negative in both the series and the magnitude of ρ_I value is smaller than that of C-5 carbon. The low magnitude and negative sign of ρ_I value for C-3 is in accordance with the fact that the σ-polarization is distance dependent and the quality of correlation is relatively insensitive to intermediate distance[11].

In both the series ρ_R values are negative for C-3 and C-5 carbons and in a series the ρ_R values are relatively constant for the two carbons. The relative constancy of ρ_R and the negative sign suggest that resonance effects transmitted by π-polarization[3,6] may be important at these two carbons.

The results of the DSP treatment indicate that the signs of the slopes for C-5 and C-4 are opposite to each other as also for C-3 and C-2. The observed alternation in signs for the slopes from C-5 to C-2 carbons is in accordance with the Pople and Gordon's prediction of bond polarization[12].

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BOOK REVIEWS

Handbook of Heterocyclic Chemistry by Alan R Katritzky (Pergamon Books Ltd, Oxford, England), 1985, pp. xxii + 542 Price $ 29.95

There has been an explosive growth in the number of heterocyclic compounds synthesised as well as in the publication of books dealing with heterocyclic chemistry, the latest being "Comprehensive Heterocyclic Chemistry" in 8 volumes with Prof A R Katritzky as Chairman of the Board of Editors. Nevertheless, the general principles of heterocyclic chemistry could still be comprehended in a "finite" volume. This Handbook of Heterocyclic Chemistry is designed to provide in one volume these basic principles governing the synthesis, structure and reactivity of heterocyclics, together with an overall picture of the subject. As stated in the foreword, this book is a sequel to the two earlier text-books, 'Heterocyclic Chemistry' (1960) and 'Principles of Heterocyclic Chemistry' (1967) by Katritzky and Lagowski. I still recall the pleasure with which I read these books soon after their publication and realised that half the chemistry of nitrogen heterocyclics can be comprehended if one understood the chemistry of the $-N=C-C$ and $-N-C=C$ bonds. This volume does bring out forcefully the highly systematic nature of the subject.

Although this Handbook has Dr Katritzky as Chairman of the Board of Editors with eight collaborators, it is evident from the uniformity of presentation that the chapters by different groups of authors have been rewritten and brought into a standard format. Thus, this book does not suffer from the drawback common to many multi-author books where each part is dealt with in a different manner and there is lack of coherence and balance in the presentation.

The book is divided into four parts. The first part, 'Preliminaries', serves as an introduction to this book as also to the Comprehensive Heterocyclic Chemistry volumes. The remaining three parts constitute the actual subject matter and deal with structure, reactivity and synthesis of heterocycles, respectively. Each part contains an overview which is followed by a treatment of individual heterocyclic systems. The emphasis in each part is on basic principles, concepts and general methodologies, thus providing a unified picture. In the part dealing with the structure of heterocycles, there are sections on nomenclature and methods for determination of structure with a great deal of emphasis on spectroscopy and X-ray analysis. Although Dr Katritzky has mentioned in the foreword that this book should be considered as Vol. 9 of Comprehensive Heterocyclic Chemistry, the present volume does stand by itself and provides a very comprehensive view of heterocyclic chemisty.

This book is by far the most authoritative one-volume account of modern heterocyclic chemistry that I have come across and gives a balanced, concise and informative account of the subject. It will be particularly suitable for MSc and PhD students and as a useful reference and guide book for teachers who in a limited time have to provide a comprehensive coverage of the subject. It will also be useful to specialists and advanced research students looking for unified overview of different heterocyclic systems and to non-specialists who require information on heterocyclic chemistry.

The book is very well produced and makes enjoyable reading.

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